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(21) International Application Number: PCT/US96/18811 (22) International Filing Date: 18 November 1996 (18.11.96) (30) Priority Data: 60/007,498 22 November 1995 (22.11.95) US 9604311.2 29 February 1996 (29.02.96) GB (71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KIM, Byeong, M. [KR/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). SHAW, Anthony, W. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). GRAHAM, Samuel, L. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). deSOLMS, S., Jane [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). CICCARONE, Terrence, M. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). (74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065 (US).	(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, HU, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE (57) Abstract The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.		

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

- 5 The Ras protein is part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is
- 10 induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem.* 62:851-
- 15 891 (1993)). Mutated *ras* genes are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.
- 20 Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa¹-Aaa²-Xaa"
- 25 box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al.*, *Nature* 310:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the
- 30 cysteine residue of the CAAX motif with a C₁₅ or C₂₀ isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem.* 61:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics* 30:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation. Other farnesylated proteins include the Ras-

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related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem.* 269, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested
5 that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been
10 demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993) and G.L. James *et al.*, *Science*, 260:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-
15 dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, 91:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo*
20 has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science* 245:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl
25 pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, 62:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, 265:14701-14704 (1990); Schafer *et al.*, *Science*, 249:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, 87:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate
30 biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

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Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et al.*, *ibid*; Reiss *et al.*, *PNAS*, 88:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, 260:1934-1937 (1993); Graham, *et al.*, *J. Med. Chem.*, 37, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been shown that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and therapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930). It has also recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516).

It is, therefore, an object of this invention to develop novel peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

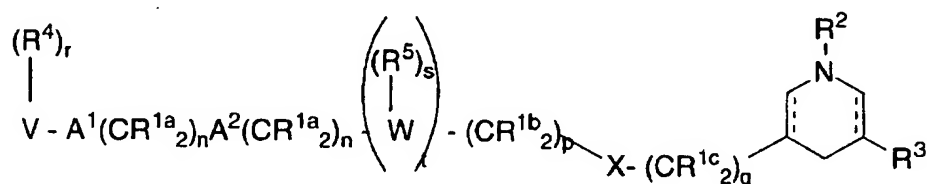
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SUMMARY OF THE INVENTION

The present invention comprises peptidomimetic piperidine, 1,4-dihydropyridine and 1,2,3,4-tetrahydropyridine compounds which inhibit the farnesyl-protein transferase.

- 5 Furthermore, these compounds differ from such heterocyclic compounds previously described as inhibitors of farnesyl-protein transferase with respect to the position of substituents about the nitrogen containing ring. Further contained in this invention are
- 10 chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

The compounds of this invention are illustrated by the formulae A:



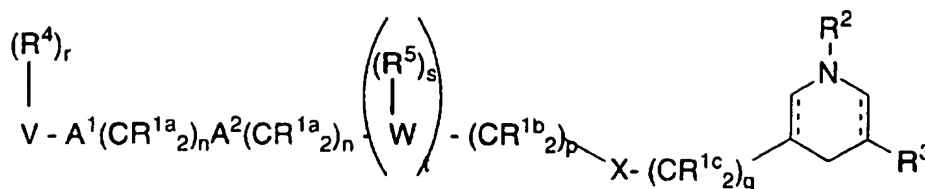
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A

DETAILED DESCRIPTION OF THE INVENTION

- 20 The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula A:

- 5 -



wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

- 5 a) hydrogen,
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)-NR⁸-;
- 15

R² is selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl,

20 unsubstituted or substituted heterocycle, $\begin{array}{c} R^6 \\ | \\ \text{C} \\ || \\ \text{O} \end{array}$, $\begin{array}{c} \text{NR}^6 R^7 \\ | \\ \text{C} \\ || \\ \text{O} \end{array}$, and -S(O)₂R⁶,

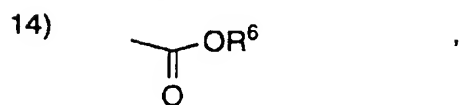
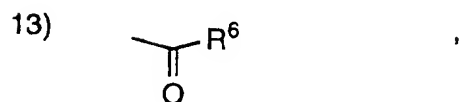
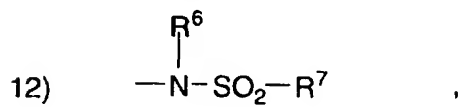
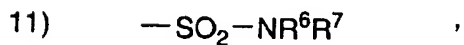
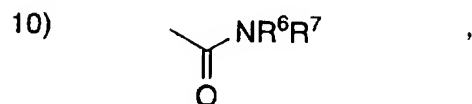
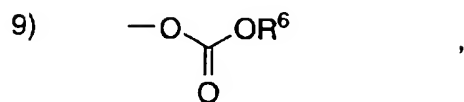
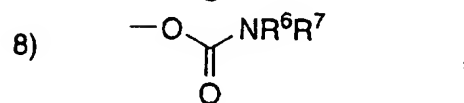
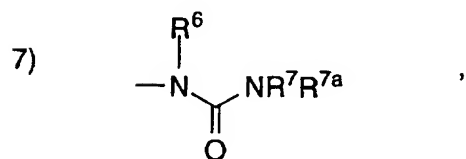
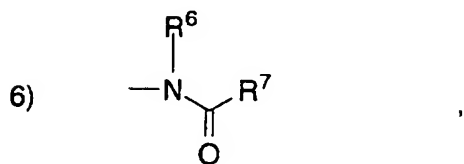
wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
 - 25 a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - c) (CH₂)_pNR⁶R⁷,
 - d) halogen,

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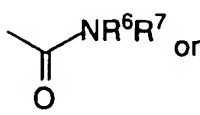
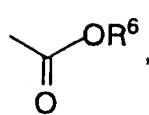
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- e) C1-4 perfluoroalkyl;
 2) C3-6 cycloalkyl,
 3) OR⁶,
 4) SR⁶, S(O)R⁶, SO₂R⁶,



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- 15) C₁₋₈ alkyl, or
 16) C₁₋₈ perfluoroalkyl;

R³ is selected from: H;  or 

5

R⁴ is independently selected from:

- a) hydrogen,
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl,
 10 C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-,
 R⁸C(O)NR⁸-, CN, NO₂, R⁸₂N-C(NR⁸)-, R⁸C(O)-,
 R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
 c) C₁₋₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆
 15 alkynyl, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-,
 R⁸C(O)NH-, CN, H₂N-C(NH)-, R⁸C(O)-, R⁸OC(O)-, N₃,
 -N(R⁸)₂, or R⁸OC(O)NH-;

R⁵ is independently selected from:

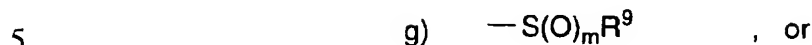
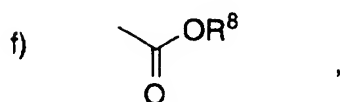
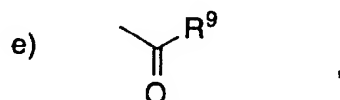
- 20 a) hydrogen,
 b) C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl,
 perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-,
 CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃,
 -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
 25 c) C₁₋₆ alkyl, unsubstituted or substituted by perfluoroalkyl,
 F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-
 C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or
 R⁹OC(O)NR⁸-;

- 30 R⁶, R⁷ and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆
 cycloalkyl, heterocycle, aryl, C₁₋₄ perfluoroalkyl, unsubstituted or
 substituted with one or two substituents selected from:

- a) C₁₋₄ alkoxy,

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- b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
- c) halogen,
- d) HO,



- h) $\text{N}(\text{R}^8)_2$; or

R^6 and R^7 may be joined in a ring;

10 R^7 and R^{7a} may be joined in a ring;

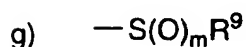
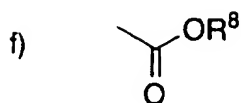
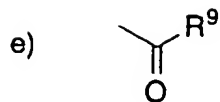
R^8 is independently selected from hydrogen, C_1 - C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

15 R^9 is independently selected from C_1 - C_6 alkyl and aryl;

R^{10} is selected from: H; $\text{R}^8\text{C}(\text{O})-$; $\text{R}^9\text{S}(\text{O})_m-$; unsubstituted or substituted C_1 -4 alkyl, unsubstituted or substituted C_3 -6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- a) C_1 -4 alkoxy,
- 25 b) aryl or heterocycle,
- c) halogen,
- d) HO,

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h) $\text{N(R}^8)_2$, or

i) C₃₋₆ cycloalkyl;

5

A¹ and A² are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C(O)}-$, $-\text{C(O)NR}^8-$, $-\text{NR}^8\text{C(O)}-$, O, $-\text{N(R}^8)-$, $-\text{S(O)}_2\text{N(R}^8)-$, $-\text{N(R}^8)\text{S(O)}_2-$, or S(O)_m ;

10 V is selected from:

a) hydrogen,

b) heterocycle,

c) aryl,

d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are

15

replaced with a heteroatom selected from O, S, and N,
and

e) C₂-C₂₀ alkenyl,

provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m ;

20

W is a heterocycle;

X is a bond, $-\text{C(=O)NR}^{10}-$, $-\text{NR}^{10}\text{C(=O)}-$, $-\text{S(O)}_m-$, $-\text{NR}^{10}-$, O or $-\text{C(=O)}-$;

25

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

- 10 -

q is 0, 1, 2, 3 or 4;
 r is 0 to 5, provided that r is 0 when V is hydrogen;
 s is 1 or 2;
 t is 0 or 1; and

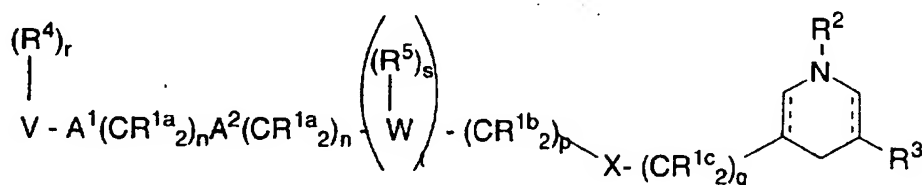
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the dashed lines represent optional double bonds;

or an optical isomer or a pharmaceutically acceptable salt thereof.

10

A preferred embodiment of the compounds of this invention is illustrated by the following formula:



A

wherein:

15 R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 20 a) hydrogen,
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₆ cycloalkyl, R⁸O-, -N(R⁸)₂ or C₂-C₆ alkenyl,
 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, R⁸O-, or -N(R⁸)₂;
- 25

R² is selected from:

- 11 -

a) C₁-8 alkyl, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

5

i) C₁-4 alkyl,

ii) (CH₂)_pOR⁶,

iii) (CH₂)_pNR⁶R⁷,

iv) halogen,

v) C₁-4 perfluoroalkyl,

10

2) OR⁶,

3) SR⁶, SO₂R⁶, or

4)  NR⁶R⁷ ;

b)  ,

15

c) aryl, unsubstituted or substituted with one or more of:

1) C₁-8 alkyl,

2) C₁-8 perfluoroalkyl,

20

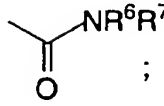
3) OR⁶,

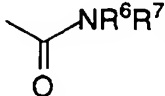
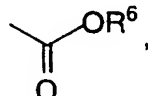
4) SR⁶, SO₂R⁶, or

5)  NR⁶R⁷ ;

d) -SO₂R⁶, and

25

e)  ;

 or  ,

R³ is selected from: H;

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R⁴ is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂,
5 (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

10

R⁵ is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN,
15 NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or
20 R⁹OC(O)NR⁸-;

20

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

25

- a) C₁-4 alkoxy,
- b) halogen, or
- c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,

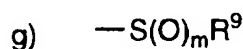
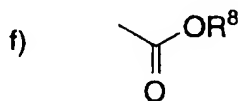
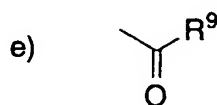
30 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

- 13 -

- R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_{1-4} alkyl, unsubstituted or substituted C_{3-6} cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- 10 a) C_{1-4} alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,



- 15 h) $N(R^8)_2$, or
i) C_{3-6} cycloalkyl;

A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^8-$, O, $-N(R^8)-$, or $S(O)_m$;

- 20 V is selected from:

- a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and
b) aryl;

25

- 14 -

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

5 X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 1, 2 or 3;

10 q is 0 or 1;

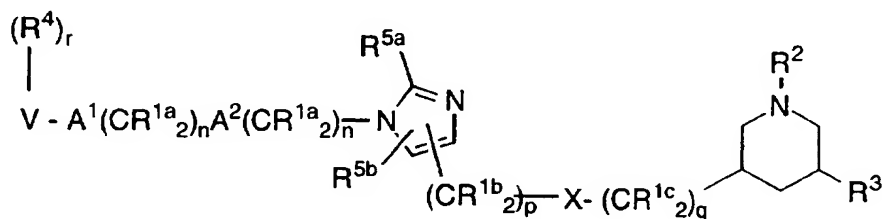
r is 0 to 5, provided that r is 0 when V is hydrogen;

s is 1 or 2; and

t is 1;

15 or an optical isomer or a pharmaceutically acceptable salt thereof.

Another preferred embodiment of the compounds of this invention are illustrated by the formula B:



20

B

wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

25

R^{1b} is independently selected from:

a) hydrogen,

- 15 -

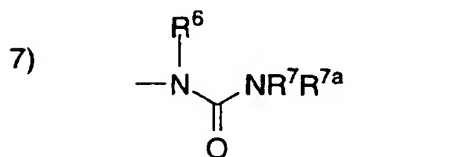
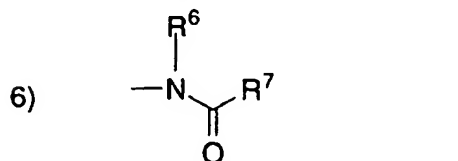
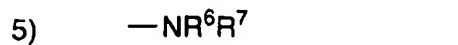
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
- c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O- and -N(R⁸)₂;

R² is selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl,

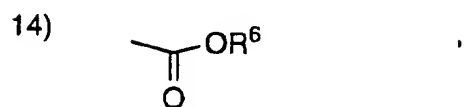
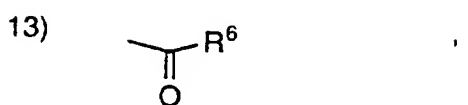
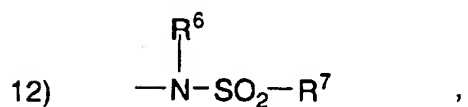
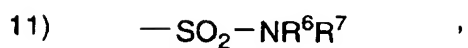
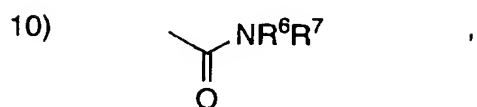
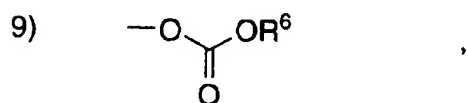
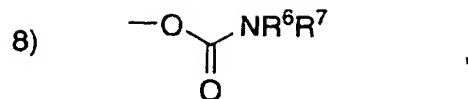
- 10 unsubstituted or substituted heterocycle, , , and -S(O)₂R⁶,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
- 15 a) C₁-4 alkyl,
 b) (CH₂)_pOR⁶,
 c) (CH₂)_pNR⁶R⁷,
 d) halogen,
 e) C₁-4 perfluoroalkyl,
- 20 2) C₃-6 cycloalkyl,
 3) OR⁶,
 4) SR⁶, S(O)R⁶, SO₂R⁶,



- 16 -



15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5

R³ is selected from: H; $\text{—C(=O)—NR}^6\text{R}^7$ or —C(=O)—OR^6 ,

R⁴ is independently selected from:

- 10 a) hydrogen,
- b) aryl, substituted aryl, heterocycle, substituted heterocycle,
 C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
 perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂,
 (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
 15 and

- 17 -

- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

- 5 R^{5a} and R^{5b} are independently hydrogen, C₁-C₆ alkyl, cyclopropyl, trifluoromethyl and halogen;

R⁶, R⁷ and R^{7a} are independently selected from:

- 10 H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

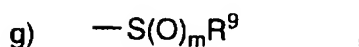
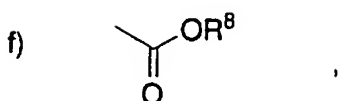
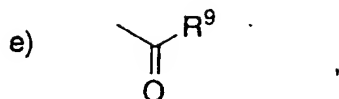
- 15 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

- 20 R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or substituted C₁-4 alkyl, unsubstituted or substituted C₃-6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl,
25 substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- 30 a) C₁-4 alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

- 18 -



h) $\text{N}(\text{R}^8)_2$, or

i) C₃₋₆ cycloalkyl;

5

A¹ and A² are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C}(\text{O})-$, $-\text{C}(\text{O})\text{NR}^8-$, O, $-\text{N}(\text{R}^8)-$, or $\text{S}(\text{O})_m$;

V is selected from:

10

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

15

c) aryl,

d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C₂-C₂₀ alkenyl, and

20

provided that V is not hydrogen if A¹ is $\text{S}(\text{O})_m$ and V is not hydrogen if A¹ is a bond, n is 0 and A² is $\text{S}(\text{O})_m$;

X is a bond, $-\text{C}(=\text{O})\text{NR}^{10}-$, $-\text{NR}^{10}\text{C}(=\text{O})-$, $-\text{S}(\text{O})_m-$ or $-\text{NR}^{10}-$;

25

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

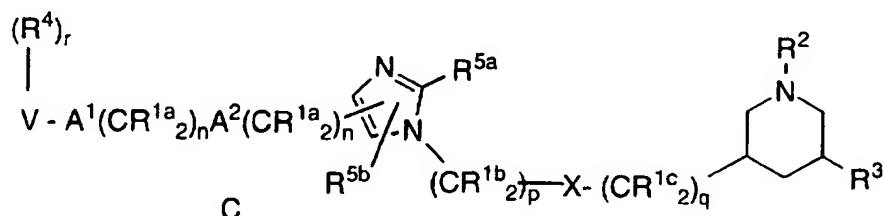
q is 0 or 1; and

- 19 -

r is 0 to 5, provided that r is 0 when V is hydrogen;

or an optical isomer or pharmaceutically acceptable salt thereof.

- 5 Another preferred embodiment of the compounds of this invention are illustrated by the formula C:



wherein:

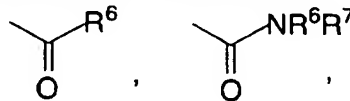
- 10 R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 15 a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
 c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from
 20 unsubstituted or substituted aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O- and -N(R⁸)₂;

R² is selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted

- 25 aryl, unsubstituted or substituted heterocycle, and -S(O)₂R⁶,



wherein the substituted group is substituted with one or more of:

- 20 -

1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:

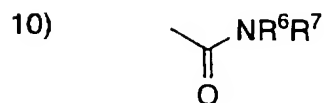
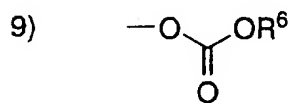
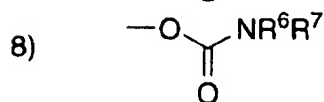
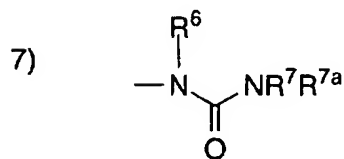
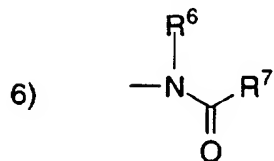
- a) C₁₋₄ alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- e) C₁₋₄ perfluoroalkyl,

2) C₃₋₆ cycloalkyl,

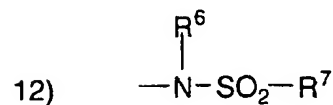
3) OR⁶,

4) SR⁶, S(O)R⁶, SO₂R⁶,

5) —NR⁶R⁷



11) —SO₂—NR⁶R⁷



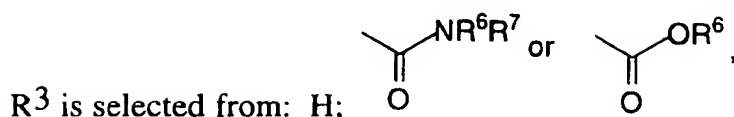
- 21 -



15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5



R⁴ is independently selected from:

- 10 a) hydrogen,
- b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 15 c) C₁₋₆ alkyl substituted by C₁₋₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

20 R^{5a} and R^{5b} are independently hydrogen, C₁₋₆ alkyl, cyclopropyl, trifluoromethyl and halogen;

R⁶, R⁷ and R^{7a} are independently selected from:

- H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
- 25 a) C₁₋₄ alkoxy,
- b) halogen, or
- c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

- 22 -

R^8 is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C₁-C₆ alkyl and aryl;

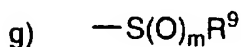
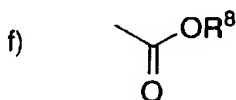
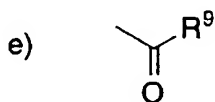
5

R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C₁-4 alkyl, unsubstituted or substituted C₃-6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

10

- a) C₁-4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,

15



h) $N(R^8)_2$, or

20

i) C₃-6 cycloalkyl;

A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^8-$, O, $-N(R^8)-$, or $S(O)_m$;

25 V is selected from:

- a) hydrogen,

- 23 -

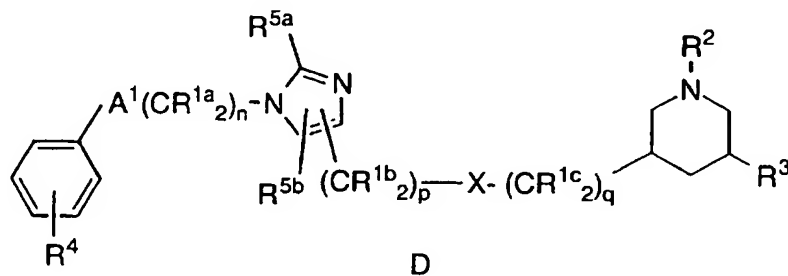
- b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,
- 5 c) aryl,
- d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and
- e) C₂-C₂₀ alkenyl, and
- 10 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

X is a bond, -C(=O)NR¹⁰-, -NR¹⁰C(=O)-, -S(O)_m- or -NR¹⁰-;

- 15 m is 0, 1 or 2;
- n is 0, 1, 2, 3 or 4;
- p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, -NR⁸- or O;
- q is 0 or 1; and
- 20 r is 0 to 5, provided that r is 0 when V is hydrogen;

or an optical isomer or pharmaceutically acceptable salt thereof.

- 25 In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula D:



wherein:

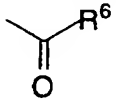
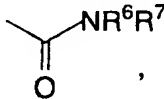
- 24 -

R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl or C₁-C₆ alkyl;

5 R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
- 10 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O-, or -N(R⁸)₂;

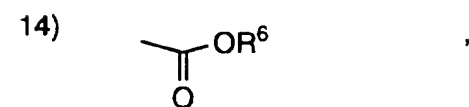
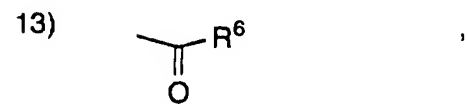
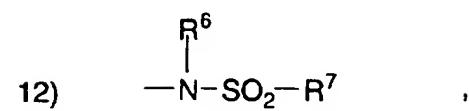
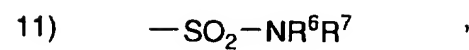
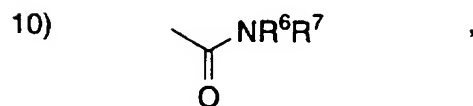
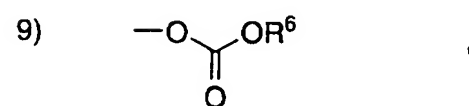
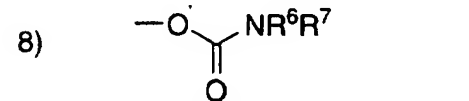
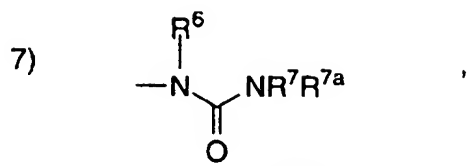
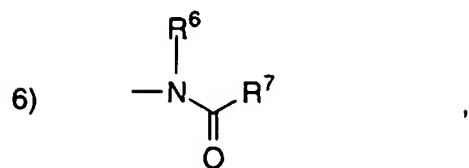
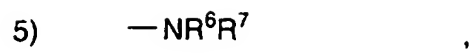
R² is selected from: H; unsubstituted or substituted C₁-8 alkyl,

unsubstituted or substituted aryl, , , and -S(O)₂R⁶,

15 wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
 - a) C₁-4 alkyl,
 - b) (CH₂)_pOR⁶,
 - 20 c) (CH₂)_pNR⁶R⁷,
 - d) halogen,
 - e) C₁-4 perfluoroalkyl,
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 25 4) SR⁶, S(O)R⁶, SO₂R⁶,

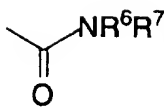
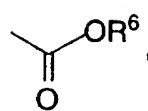
- 25 -



5

15) C₁₋₈ alkyl, or16) C₁₋₈ perfluoroalkyl;

- 26 -

R³ is selected from: H;  or .

R⁴ is independently selected from:

- a) hydrogen,
- 5 b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

15 R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R⁶, R⁷ and R^{7a} are independently selected from:

- H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
- a) C₁-4 alkoxy,
 - 20 b) halogen, or
 - c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

25 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R⁹ is independently selected from C₁-C₆ alkyl and aryl;

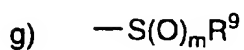
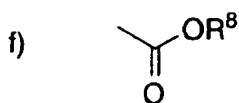
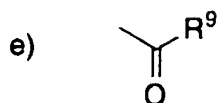
30 R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or substituted C₁-4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

- a) C₁-4 alkoxy,
- b) aryl or heterocycle,

- 27 -

c) halogen,

d) HO,



5

h) $N(R^8)_2$, ori) C₃₋₆ cycloalkyl;

A¹ is selected from: a bond, -C(O)-, O, -N(R⁸)-, or S(O)_m;

10 X is a bond, -C(=O)NR¹⁰-, -NR¹⁰C(=O)-, -S(O)_m- or -NR¹⁰-;

n is 0 or 1; provided that n is not 0 if A¹ is a bond, O, -N(R⁸)-, or S(O)_m;

m is 0, 1 or 2;

15 p is 0, 1, 2, 3 or 4; and

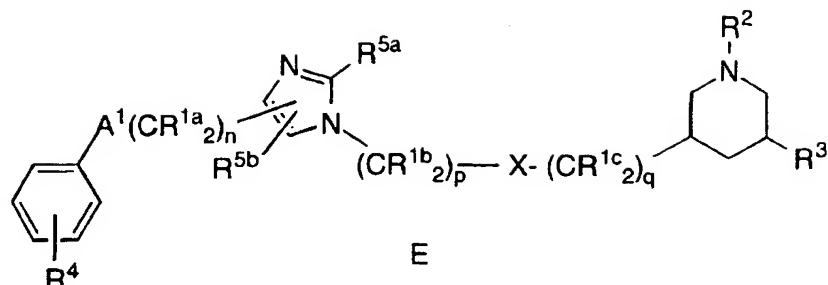
q is 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

20

In another more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula E:

- 28 -



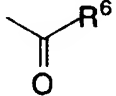
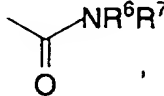
wherein:

5 R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O- ,
 $-N(R^8)_2$, F, C3-C10 cycloalkyl or C1-C6 alkyl;

R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) aryl, heterocycle, C3-C10 cycloalkyl, R^8O- , $-N(R^8)_2$, F or
 C2-C6 alkenyl,
 c) C1-C6 alkyl unsubstituted or substituted by aryl,
 heterocycle, C3-C10 cycloalkyl, C2-C6 alkenyl, R^8O- , or
 $-N(R^8)_2$;

15 R^2 is selected from: H; unsubstituted or substituted C1-8 alkyl,

unsubstituted or substituted aryl, , , and $-S(O)_2R^6$,

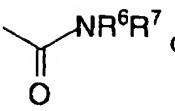
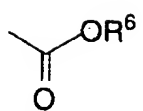
wherein the substituted group is substituted with one or more of:

- 20 1) aryl or heterocycle, unsubstituted or substituted with
 one or two groups selected from:
 a) C1-4 alkyl,
 b) $(CH_2)_pOR^6$,
 c) $(CH_2)_pNR^6R^7$,
 d) halogen,
 e) C1-4 perfluoroalkyl,
 25 2) C3-6 cycloalkyl,
 3) OR^6 ,

- 29 -

4) SR^6 , S(O)R^6 ; SO_2R^6 ,5) $-\text{NR}^6\text{R}^7$,6)
$$\begin{array}{c} \text{R}^6 \\ | \\ -\text{N}-\text{C}(=\text{O})-\text{R}^7 \\ | \\ \text{O} \end{array}$$
 ,7)
$$\begin{array}{c} \text{R}^6 \\ | \\ -\text{N}-\text{C}(=\text{O})-\text{NR}^7\text{R}^{7a} \\ | \\ \text{O} \end{array}$$
 ,8)
$$\begin{array}{c} -\text{O}-\text{C}(=\text{O})-\text{NR}^6\text{R}^7 \\ | \\ \text{O} \end{array}$$
 ,9)
$$\begin{array}{c} -\text{O}-\text{C}(=\text{O})-\text{OR}^6 \\ | \\ \text{O} \end{array}$$
 ,10)
$$\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}(=\text{O})-\text{NR}^6\text{R}^7 \\ | \\ \text{O} \end{array}$$
 ,11) $-\text{SO}_2-\text{NR}^6\text{R}^7$,12)
$$\begin{array}{c} \text{R}^6 \\ | \\ -\text{N}-\text{SO}_2-\text{R}^7 \end{array}$$
 ,13)
$$\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}(=\text{O})-\text{R}^6 \\ | \\ \text{O} \end{array}$$
 ,14)
$$\begin{array}{c} \text{CH}_3 \\ | \\ \text{C}(=\text{O})-\text{OR}^6 \\ | \\ \text{O} \end{array}$$
 ,15) C₁₋₈ alkyl, or16) C₁₋₈ perfluoroalkyl;

- 30 -

R³ is selected from: H;  or .

R⁴ is independently selected from:

- a) hydrogen,
- 5 b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

15 R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R⁶, R⁷ and R^{7a} are independently selected from:

- H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
- a) C₁-4 alkoxy,
 - 20 b) halogen, or
 - c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

25 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

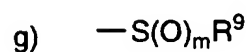
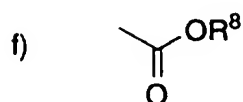
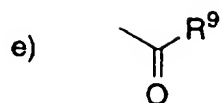
R⁹ is independently selected from C₁-C₆ alkyl and aryl;

30 R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or substituted C₁-4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

- a) C₁-4 alkoxy,
- b) aryl or heterocycle,

- 31 -

- c) halogen,
d) HO,



- 5 h) $\text{N(R}^8)_2$, or
i) C₃₋₆ cycloalkyl;

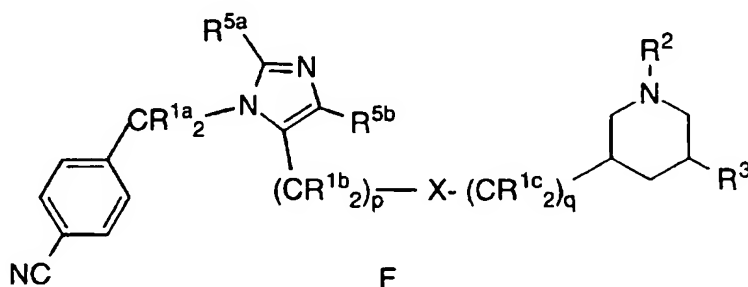
X is a bond, $-\text{C(=O)NR}^{10}-$, $-\text{NR}^{10}\text{C(=O)}-$, $-\text{S(O)}_m-$ or $-\text{NR}^{10}-$;

- 10 n is 0 or 1;
m is 0, 1 or 2;
p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond,
 $-\text{NR}^8-$ or O; and
q is 0 or 1;

15 or an optical isomer or pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of
farnesyl-protein transferase are illustrated by the formula F:

20



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wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl or C₁-C₆ alkyl;

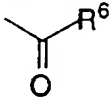
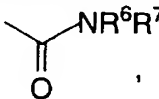
5

R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂ or F,
- c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, or -N(R⁸)₂;

10

R² is selected from: H; unsubstituted or substituted C₁-8 alkyl,

unsubstituted or substituted aryl, , , and -S(O)₂R⁶,

wherein the substituted group is substituted with one or more of:

15

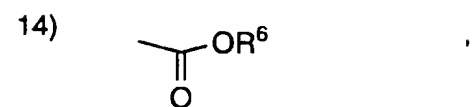
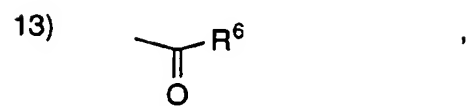
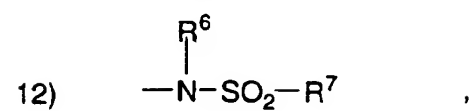
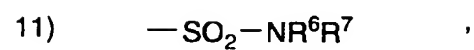
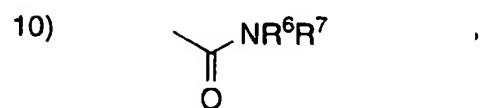
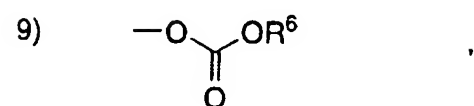
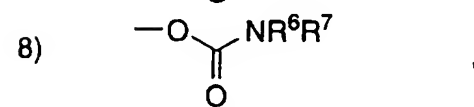
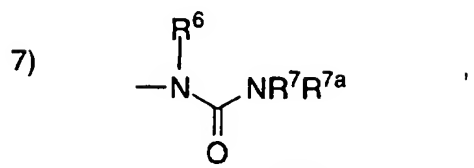
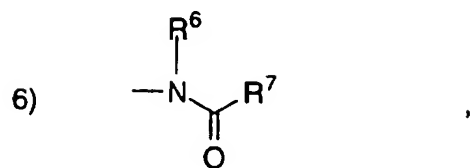
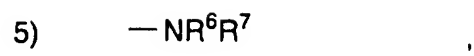
- 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:

20

- a) C₁-4 alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- e) C₁-4 perfluoroalkyl,
- 2) C₃-6 cycloalkyl,
- 3) OR⁶,
- 4) SR⁶, S(O)R⁶, SO₂R⁶,

25

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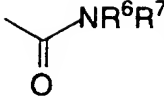
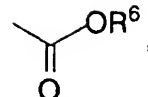


5

15) C1-8 alkyl, or

16) C1-8 perfluoroalkyl;

- 34 -

R³ is selected from: H;  or .

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

5 R⁶, R⁷ and R^{7a} are independently selected from:
H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

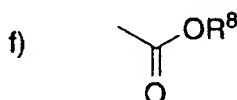
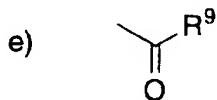
- 10 a) C₁-4 alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or
unsubstituted heterocycle;

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-
trifluoroethyl, benzyl and aryl;

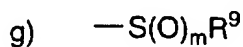
15 R⁹ is independently selected from C₁-C₆ alkyl and aryl;

R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or
substituted C₁-4 alkyl, wherein the substituted alkyl group is substituted
20 with one or two substituents selected from:

- a) C₁-4 alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,



25



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- h) $N(R^8)_2$, or
- i) C₃₋₆ cycloalkyl;

5 X is a bond, $-C(=O)NR^{10}$ -, $-NR^{10}C(=O)$ -, $-S(O)_m$ - or $-NR^{10}$ -;

m is 0, 1 or 2;

p is 0, 1, 2, 3 or 4; and

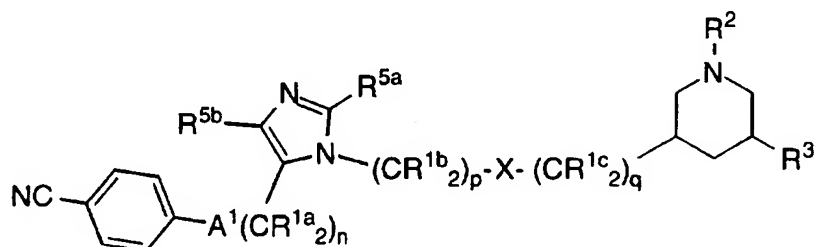
q is 0 or 1;

10

or an optical isomer or pharmaceutically acceptable salt thereof.

In a further embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula G:

15



G

wherein:

20 R^{1a} and R^{1c} are independently selected from: hydrogen, R^8O -, $-N(R^8)_2$, F, C₃₋₁₀ cycloalkyl or C₁₋₆ alkyl;

R^{1b} is independently selected from:

- a) hydrogen,
- b) aryl, heterocycle or C₃₋₁₀ cycloalkyl,
- 25 c) C₁₋₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, R^8O -, or $-N(R^8)_2$;

- 36 -

R^2 is selected from: H; unsubstituted or substituted C_{1-8} alkyl,

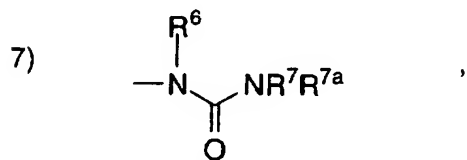
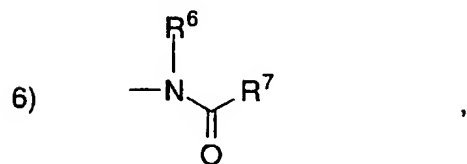
unsubstituted or substituted aryl, $\text{C}(=\text{O})\text{R}^6$, $\text{C}(=\text{O})\text{NR}^6\text{R}^7$, and $-\text{S}(\text{O})_2\text{R}^6$,
 wherein the substituted group is substituted with one or more of:

5 1) aryl or heterocycle, unsubstituted or substituted with
 one or two groups selected from:

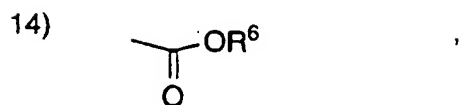
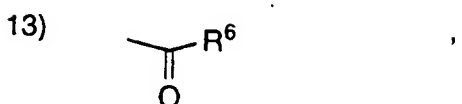
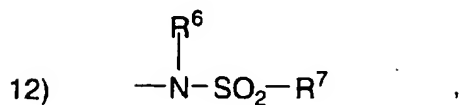
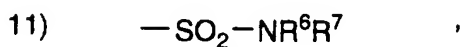
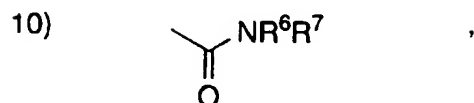
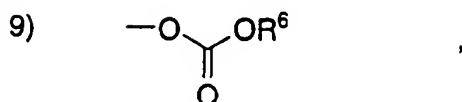
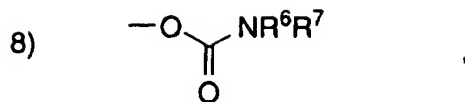
- 10 a) C_{1-4} alkyl,
 b) $(\text{CH}_2)_p\text{OR}^6$,
 c) $(\text{CH}_2)_p\text{NR}^6\text{R}^7$,
 d) halogen,
 e) C_{1-4} perfluoroalkyl,

- 2) C_{3-6} cycloalkyl,
 3) OR^6 ,
 4) SR^6 , $\text{S}(\text{O})\text{R}^6$, SO_2R^6 ,

- 15 5) $-\text{NR}^6\text{R}^7$,



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15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

R³ is selected from: H; $\text{—C(=O)—NR}^6\text{R}^7$ or —C(=O)—OR^6 ,

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

a) C₁₋₄ alkoxy,

b) halogen, or

- 38 -

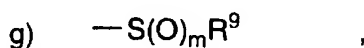
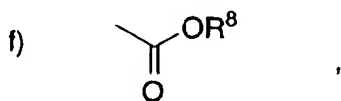
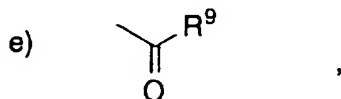
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

5 R^8 is independently selected from hydrogen, C_1 - C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1 - C_6 alkyl and aryl;

10 R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_1 -4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

- 15 a) C_1 -4 alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,



h) $N(R^8)_2$, or

i) C_3 -6 cycloalkyl;

20

A^1 is selected from: a bond, $-C(O)-$, O, $-N(R^8)-$, or $S(O)_m$;

X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

25 m is 0, 1 or 2;

n is 0 or 1;

p is 1, 2 or 3; and

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q is 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

5 The preferred compounds of this invention are as follows:

1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-
1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

1-(1-Naphthylmethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-
1H-imidazol-5-ylethyl)carbamoyl] piperidine

15

1-Benzyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-
5-ylethyl)carbamoyl] piperidine

1-Methyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-
20 5-ylethyl)carbamoyl] piperidine

1-(2-Indanyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(2-Diphenylethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-
1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Phenylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

30

1-(2-Methylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

1-Phenethyl-*cis*-3-carboxyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
35 ylethyl)carbamoyl] piperidine

- 40 -

1-Phenethyl-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine

5 1-Phenethyl-*cis*-3-[N-(benzyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-Phenethyl-*cis*-3-[N-(cyclopropyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-Phenethyl-*cis*-3-[N-(*t*-butyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-(2,2-Diphenylethyl)-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-*cis*-3-[N-(*t*-butyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 N-[1-Phenethyl-*cis*-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamyl] piperidine-3-carbonyl] methionine methyl ester

N-[1-Phenethyl-*cis*-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamyl] piperidine-3-carbonyl] methionine

25 1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine

30 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine

1-Diphenylacetyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(*t*-Butoxycarbonyl)-*trans*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]-piperidine

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1-(2,2-Diphenylethyl)-3-[N-1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylpropionyl)amino] piperidine

10 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylcarbonyl)amino] piperidine

15 1-(Phenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(Diphenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(3-Chlorobenzoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(3-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(Dibenzylsuberylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2-(3-Methylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(3-Trifluoromethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(2-(2-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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1-(2-(4-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2-(3-Aminomethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Phenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-(2-Phenethyl)-3(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-(3-Phenylpropyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Benzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(2-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(3-Chlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2,2-Diphenyl-2-hydroxyethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Methoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(3,5-Dichlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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1-(3-Trifluoromethoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2,5-Dimethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Trifluoromethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-(3-Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-Isobutyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(2-Methyl-2-phenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(2-(1-Piperidinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-methoxybenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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- 1-(3-Methoxyphenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 5 1-(1-Naphthylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(3-Chlorophenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 10 1-(α -Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 15 1-(α -Toluenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(Benzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 20 1-(1-Naphthylenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 25 1-(3-Chlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(3,5-Dichlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 30 1-(α -Toluenesulfonyl)-3(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(α -Toluenesulfonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 35

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- 1-(Methanesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 5 1-(Diphenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(Phenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 10 1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl]-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 15 1-(2-Pyridylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-Phenyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 20 1-(3-Methylphenyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(2,2-Diphenylethyl)-3(S)-[2-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethylthiomethyl] piperidine
- 25 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethylsulfonylmethyl] piperidine
- 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-methyl-carbamoyl] piperidine
- 30 1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)N-methyl-carbamoyl] piperidine
- 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)aminomethyl] piperidine
- 35 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

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1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-cyclopropylmethyl-aminomethyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(2-methyl-1H-imidazol-4-ylethyl)-N-(4-cyanobenzoyl)aminomethyl] piperidine

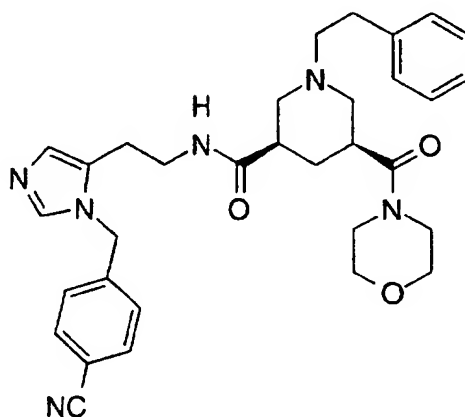
10 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylmethyl] piperidine

15 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylethylcarbamoyl] piperidine

or an optical isomer or a pharmaceutically acceptable salt thereof.

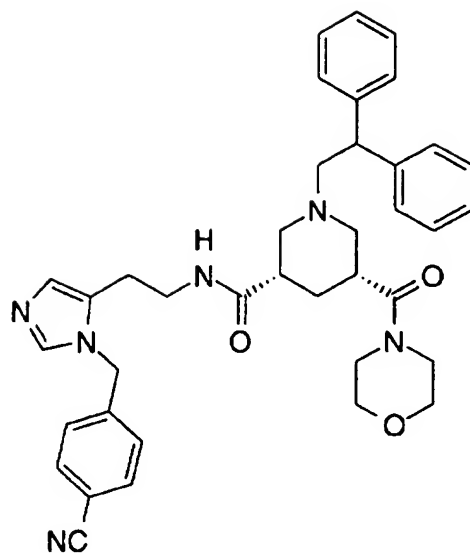
Specific examples of the compounds of the invention are:

20 1-Phenethyl-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine



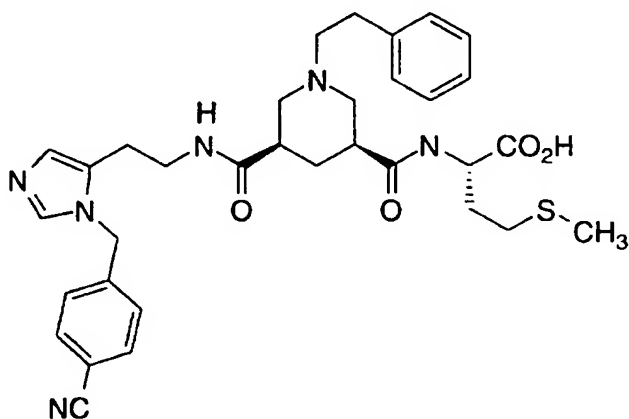
25 1-(2-Diphenylethyl)-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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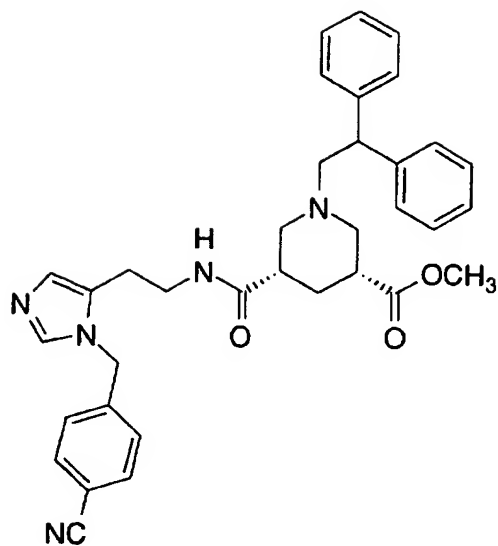
N-[1-Phenethyl-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamyl]
piperidine-*cis*-3-carbonyl] methionine

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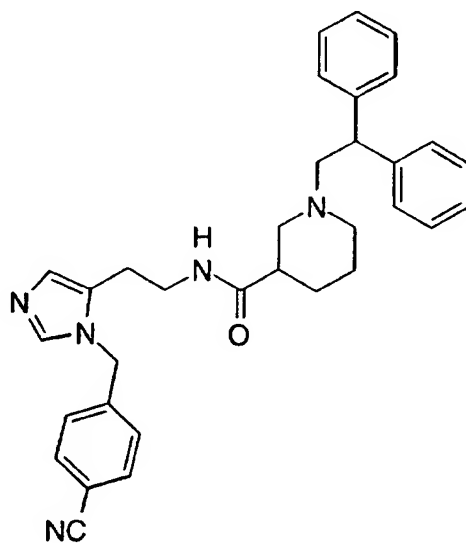
1-(2-Diphenylethyl)-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-
imidazole-*cis*-5-ethyl)carbamoyl] piperidine

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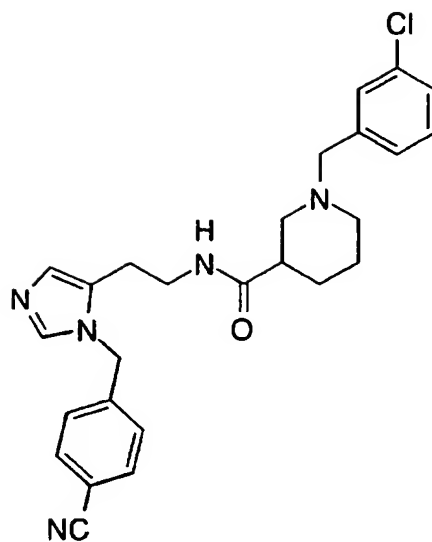
1-(2,2-Diphenylethyl)-*cis*-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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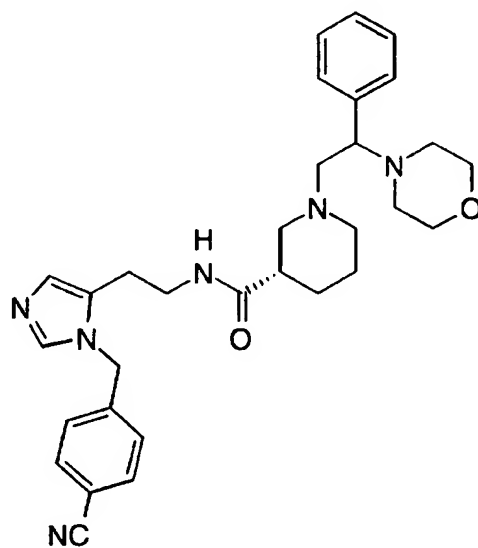


1-(3-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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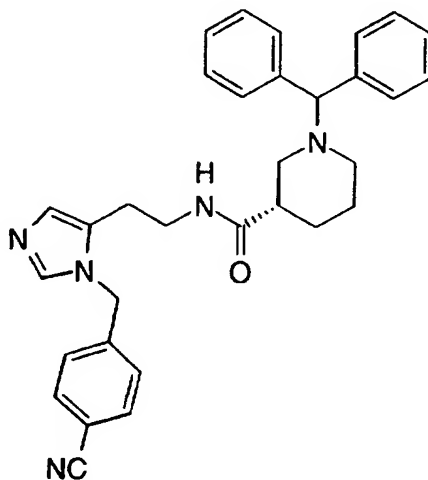


1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-
5 imidazol-5-ylethyl)carbamoyl] piperidine

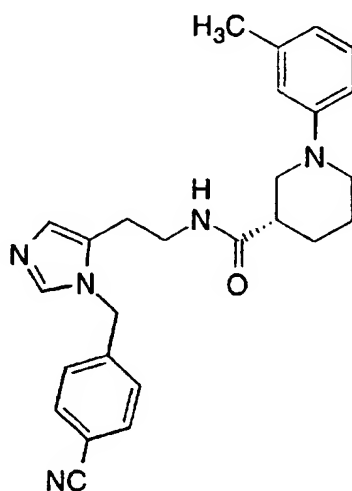


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1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine

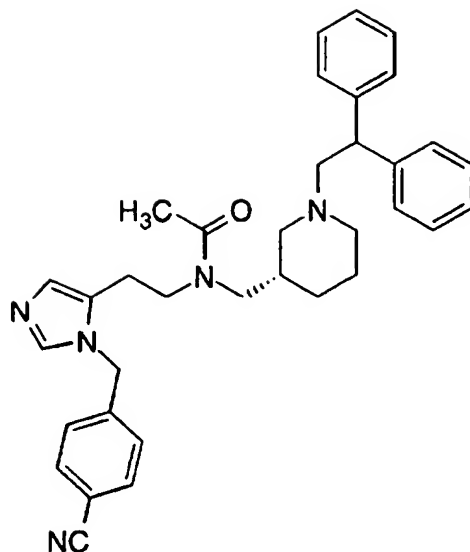


5 1-(3-Methylphenyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine



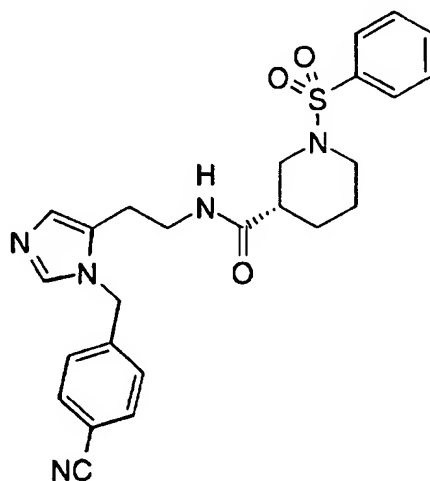
10 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

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1-(Benzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5



or an optical isomer or a pharmaceutically acceptable salt thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical

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isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^{1a}, R⁴ etc.) occurs more than one time in any constituent, its definition on each occurrence is independent at every other occurrence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

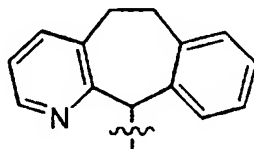
As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of monocyclic and bicyclic aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl. Examples of tricyclic aryl elements include 10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl (which is also known as dibenzylsuberyl), 9-fluorenyl and 9,10-dihydroanthracen-9-yl. Preferably, "aryl" is a monocyclic or bicyclic carbon ring.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring or stable 13- to 15-membered tricyclic heterocyclic ring, which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of monocyclic and bicyclic heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl,

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dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolynyl, imidazolyl, indolynyl, indolyl, isochromanyl, isoindolynyl, isoquinolynyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholynyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolynyl, quinolynyl, quinoxalynyl, tetrahydrofuryl, tetrahydroisoquinolynyl, tetrahydroquinolynyl, thiamorpholynyl, thiamorpholynyl sulfoxide, thiazolyl, thiazolynyl, thienofuryl, thienothienyl, and thienyl. Examples of tricyclic heterocyclic elements include, but are not limited to, 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 9,10-dihydro-4H-3-thia-benzo[f]azulen-4-yl and 9-xanthenyl. The 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine moiety has the following structure:



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Preferably, "heterocyclic" is a monocyclic or bicyclic moiety.

As used herein, "heteroaryl" is intended to mean any stable monocyclic, bicyclic or tricyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group consisting of N, O, and S. Examples of monocyclic and bicyclic heteroaryl elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolynyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolynyl, indolyl, isochromanyl, isoindolynyl, isoquinolynyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolynyl, quinolynyl,

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quinoxaliny, tetrahydroisoquinoliny, tetrahydroquinoliny, thiazoly, thienofury, thienothieny, and thieny. Examples of tricyclic heteroaryl elements include, but are not limited to, 6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridine. Preferably, "heteroaryl" is a
5 monocyclic or bicyclic moiety.

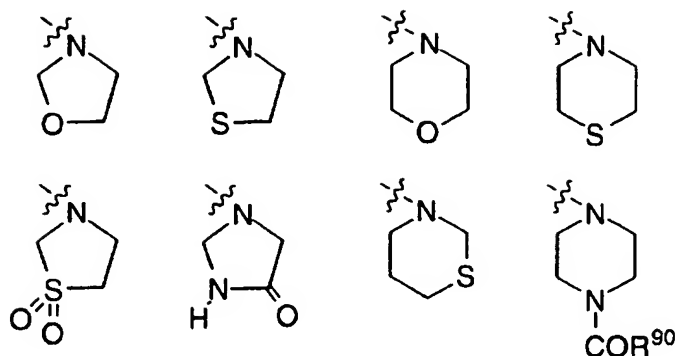
As used herein, the terms "substituted aryl", "substituted heterocycle" and "substituted cycloalkyl" are intended to include the cyclic group containing from 1 to 3 substituents in addition to the point of attachment to the rest of the compound. Such substituents are
10 preferably selected from the group which includes but is not limited to F, Cl, Br, CF₃, NH₂, N(C₁-C₆ alkyl)₂, NO₂, CN, (C₁-C₆ alkyl)O-, -OH, (C₁-C₆ alkyl)S(O)_m-, (C₁-C₆ alkyl)C(O)NH-, H₂N-C(NH)-, (C₁-C₆ alkyl)C(O)-, (C₁-C₆ alkyl)OC(O)-, N₃, (C₁-C₆ alkyl)OC(O)NH- and C₁-C₂₀ alkyl.

15 When R⁶ and R⁷ or R⁷ and R^{7a} are combined to form a ring, cyclic amine moieties are formed. Examples of such cyclic moieties include, but are not limited to:



20 In addition, such cyclic moieties may optionally include another heteroatom(s). Examples of such heteroatom-containing cyclic amine moieties include, but are not limited to:

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Lines drawn into the ring systems from substituents (such as from R^2 , R^3 , R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

5

Preferably, R^{1a} and R^{1b} are independently selected from: hydrogen, $-N(R^8)_2$, $R^8C(O)NR^8-$ or C_1 - C_6 alkyl which is unsubstituted or substituted by $-N(R^8)_2$, R^8O- or $R^8C(O)NR^8-$.

Preferably, R^2 is selected from:

10

a) C_{1-8} alkyl, unsubstituted or substituted with one or more of:

1) aryl or heterocycle, unsubstituted or substituted with:

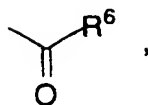
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- i) C_{1-4} alkyl,
- ii) $(CH_2)_pOR^6$,
- iii) $(CH_2)_pNR^6R^7$,
- iv) halogen,
- v) C_{1-4} perfluoroalkyl,

20

- 2) OR^6 ,
- 3) SR^6 , SO_2R^6 , or
- 4) $\begin{array}{c} \text{CH}_3 \\ | \\ \text{C} \\ || \\ \text{O} \end{array} NR^6R^7$;

b)



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c) aryl, unsubstituted or substituted with one or more of:

- 1) C₁₋₈ alkyl,
- 2) C₁₋₈ perfluoroalkyl,
- 3) OR⁶,
- 4) SR⁶, SO₂R⁶, or
- 5) $\begin{array}{c} \diagup \\ \text{C} \\ \diagdown \end{array} \text{NR}^6\text{R}^7$;

d) -SO₂R⁶.

Preferably, R² comprises at least one unsubstituted or substituted phenyl.

Preferably, R⁴ is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, CN, NO₂, R⁸₂N-C(NR⁸)-, R⁸C(O)-, N₃, -N(R⁸)₂, R⁹OC(O)NR⁸- and C₁-C₆ alkyl.

Preferably, R⁵ is hydrogen.

Preferably, R^{7b} is C₁-C₆ alkyl substituted with hydrogen or an unsubstituted or substituted aryl group.

Preferably, R⁸ is selected from H, C₁-C₆ alkyl and benzyl.

Preferably, A¹ and A² are independently selected from: a bond, -C(O)NR⁸-, -NR⁸C(O)-, O, -N(R⁸)-, -S(O)₂N(R⁸)- and -N(R⁸)S(O)₂-.

Preferably, V is selected from hydrogen, heterocycle and aryl.

Preferably, W is imidazolyl.

Preferably, X is a bond, -C(=O)NR¹⁰-, -NR¹⁰C(=O)- or -NR¹⁰-.

Preferably, n, p and r are independently 0, 1, or 2.

Preferably t is 1.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared

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from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic,
5 isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, -N(R⁸)₂ represents -NH₂, -NHCH₃, -NHC₂H₅, etc. It is understood
10 that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

15 The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric
20 amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Abbreviations used in the description of the chemistry and in the Examples that follow are:

25	Ac ₂ O	Acetic anhydride;
	Boc	t-Butoxycarbonyl;
	CBz	Carbobenzyloxy;
	DBU	1,8-diazabicyclo[5.4.0]undec-7-ene;
	DMAP	4-Dimethylaminopyridine;
30	DME	1,2-Dimethoxyethane;
	DMF	Dimethylformamide;
	EDC	1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide-hydrochloride;
	Et ₃ N	Triethylamine;

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	EtOAc	Ethyl acetate;
	FAB	Fast atom bombardment;
	HOBT	1-Hydroxybenzotriazole hydrate;
	HOObt	3-Hydroxy-1,2,2-benzotriazin-4(3 <i>H</i>)-one;
5	HPLC	High-performance liquid chromatography;
	MCPBA	m-Chloroperoxybenzoic acid;
	MsCl	Methanesulfonyl chloride;
	NaHMDS	Sodium bis(trimethylsilyl)amide;
	Py	Pyridine;
10	TFA	Trifluoroacetic acid;
	THF	Tetrahydrofuran.

The compounds of this invention are prepared by employing reactions as shown in the Schemes 1-21, in addition to other
15 standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. While stereochemistry is shown in the Schemes, a person of ordinary skill in the art would understand that the illustrated compounds represent racemic mixtures which may be
20 separated at a subsequent purification step or may be utilized as the racemic mixture.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the reductive
25 alkylation or acylation reactions described in the Schemes.

Synopsis of Schemes 1-8:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the
30 most part. In Schemes 1-3, for example, the syntheses of 1,3,5-trisubstituted piperidines are outlined. The reactions described therein may be similarly applied to suitably protected commercially available nipecotic acid or nipecotamide to provide compounds of the instant invention wherein R³ is hydrogen.

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As shown in Scheme 1, the pyridinedicarboxylic acid diester may be catalytically hydrogenated and then N-protected to provide a mixture of piperidine diesters **1**. The protected piperidine can then be partially hydrolyzed to provide a racemic mixture of 3,5-cis- and trans-isomers, that can be separated by chromatography. The remainder of Scheme 1 and Schemes 2 and 3 illustrate manipulation of the racemic mixture of the cis-isomers. It is well understood by one of ordinary skill in the art that such chemical manipulations can also be applied to the racemic mixture of the trans-isomers to obtain other compounds of the instant invention. Furthermore, such manipulations can also be applied to enantiomerically pure isomers (i.e., the (+)-cis isomer or the (-)-cis isomer). The trans-isomer may also be epimerized to the cis-isomer by treatment with a base, such as sodium carbonate. Racemic final compounds may be separated on a chiral preparative HPLC column to give their respective diastereomers.

The monocarboxylic acid **2** can be treated with an appropriately substituted amine in the presence of a suitable coupling reagent, such as EDC/HOBT, and the like, to provide the 5-carboxynipecotamide **3**. The suitably substituted 5-carboxynipecotamide is then deprotected and the piperidine nitrogen can then be reductively alkylated to provide intermediate **4**. The remaining ester moiety is saponified and then similarly functionalized with another suitably substituted amine to provide the bisamidopiperidine **5**.

An alternative synthetic route to compound **5**, starting with the carboxynipecotamide **3**, is illustrated in Scheme 2.

As shown in Scheme 3, the monocarboxylic acid **2** can undergo a Curtius rearrangement to provide the piperidine **6** after catalytic reduction. Subsequent amide formation provides intermediate **7**, which is then subjected to the reactions illustrated in Scheme 1 to provide compound **8** of the instant invention.

The instant invention also includes 1,4-dihydropyridine and 1,2,3,4-tetrahydropyridine analogs of the piperidine compounds whose syntheses are described above. Scheme 4 illustrates the synthetic route to the intermediates **11** and **13** which correspond to the saturated ring

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intermediate **2** illustrated in Scheme 1. Thus, the appropriately substituted pyridine may be N-alkylated to provide the quaternary intermediate **9**. Subsequent reduction of this intermediate provides the 1,4-dihydropyridine **10**, which can be selectively hydrolized to the key intermediate **11**. Alternatively, the 1,4-dihydropyridine **10** can be further reduced to provide the enantiomeric mixture of tetrahydropyridines **12**, which can be hydrolized and resolved by chromatography to provide the key intermediate **13** (and the enantiomer which is not illustrated). Intermediates **11** and **13** can then undergo synthetic modifications as described hereinabove in Schemes 1-3.

Schemes 5-7 illustrate the syntheses of 1,3-disubstituted piperidines of the instant invention wherein the "X" moiety is other than an amido moiety. The reactions illustrated therein may be modified by using appropriate protecting groups and reagents well known to one skilled in the art to provide 1,3,5-trisubstituted piperidines of the instant invention.

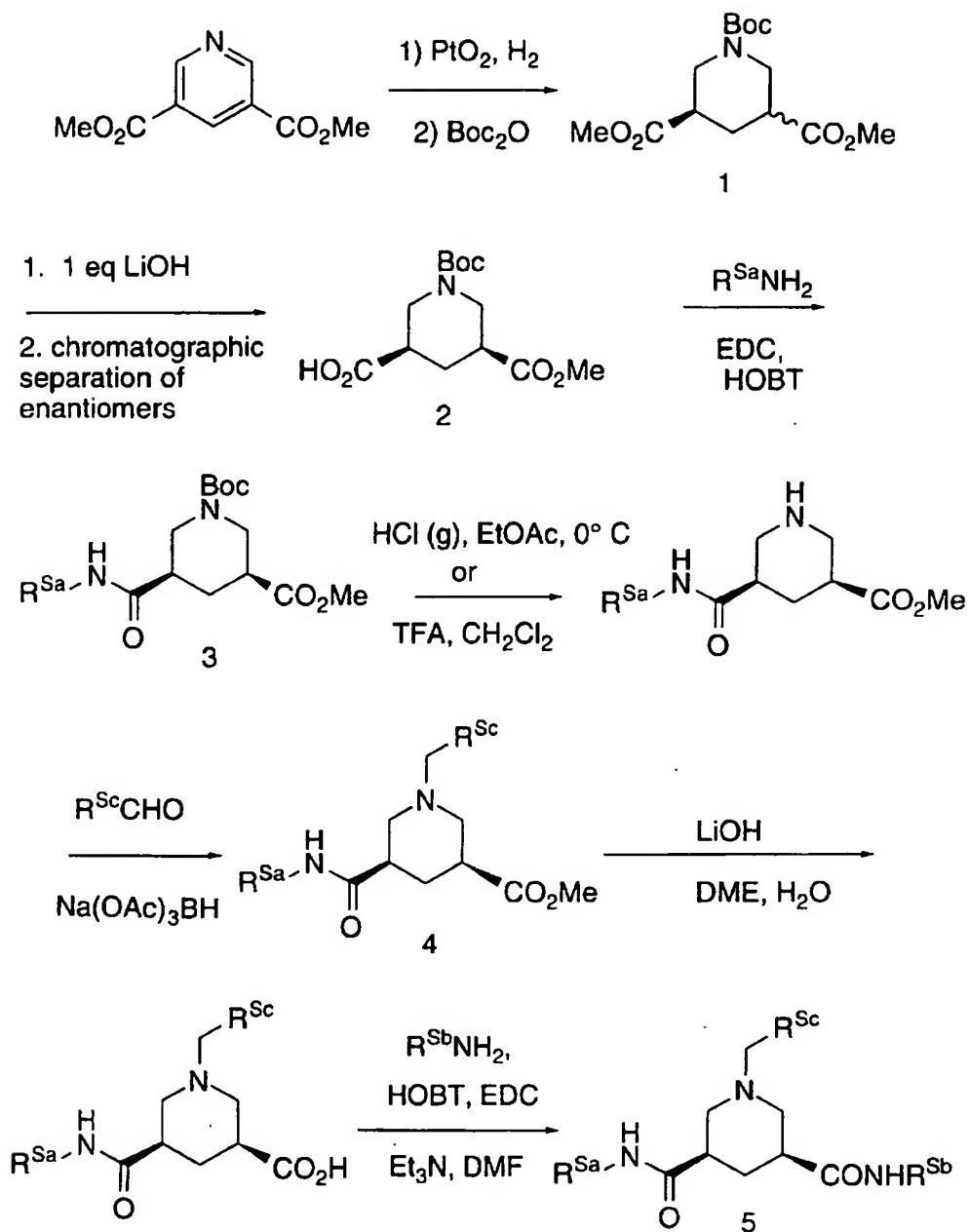
Scheme 5 illustrates the syntheses of compounds of the instant invention wherein "X" is -S- or -SO₂-. A racemic nipecotate **14** can be resolved by the selective crystallization of chiral tartrate salts and is then reductively alkylated to provide the ester **15**. Intermediate **15** is reduced to the alcohol **16**, activated and treated with a suitable thioacetate to provide the thioester **17**. The thiol is then generated and may be alkylated and optionally oxidized to provide compounds **18** and **19** of the instant invention.

The intermediate **16** may be selectively oxidized back to an aldehyde, which can then be utilized to reductively alkylate a suitably substituted amine to provide the instant compound **20**. The secondary amine of **20** can be further functionalized as illustrated.

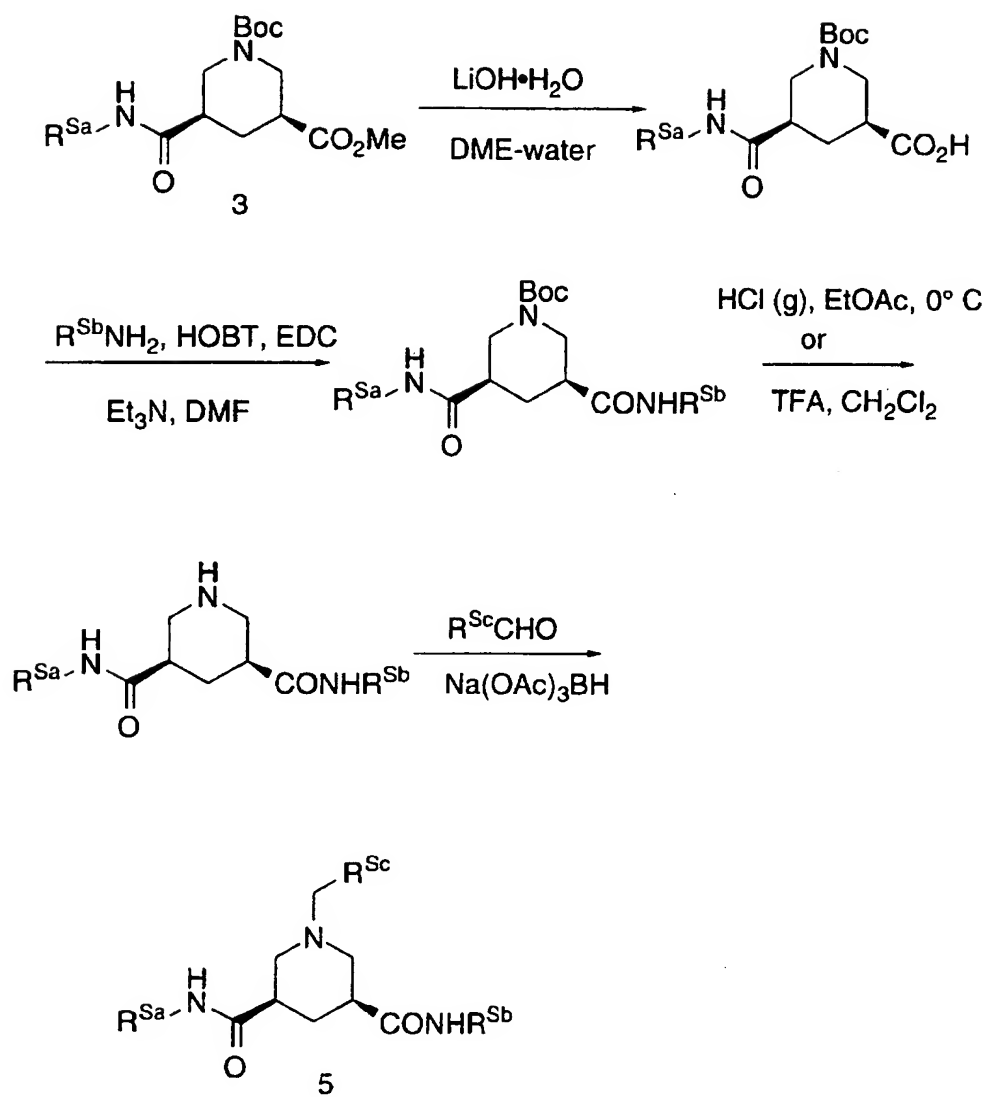
The activated alcohol can also be reacted with a suitably substituted imidazolyl to provide compounds of the instant invention wherein "X" is a bond, as shown in Scheme 7.

Scheme 8 illustrates the syntheses of compounds of the instant invention wherein R² is an aryl moiety.

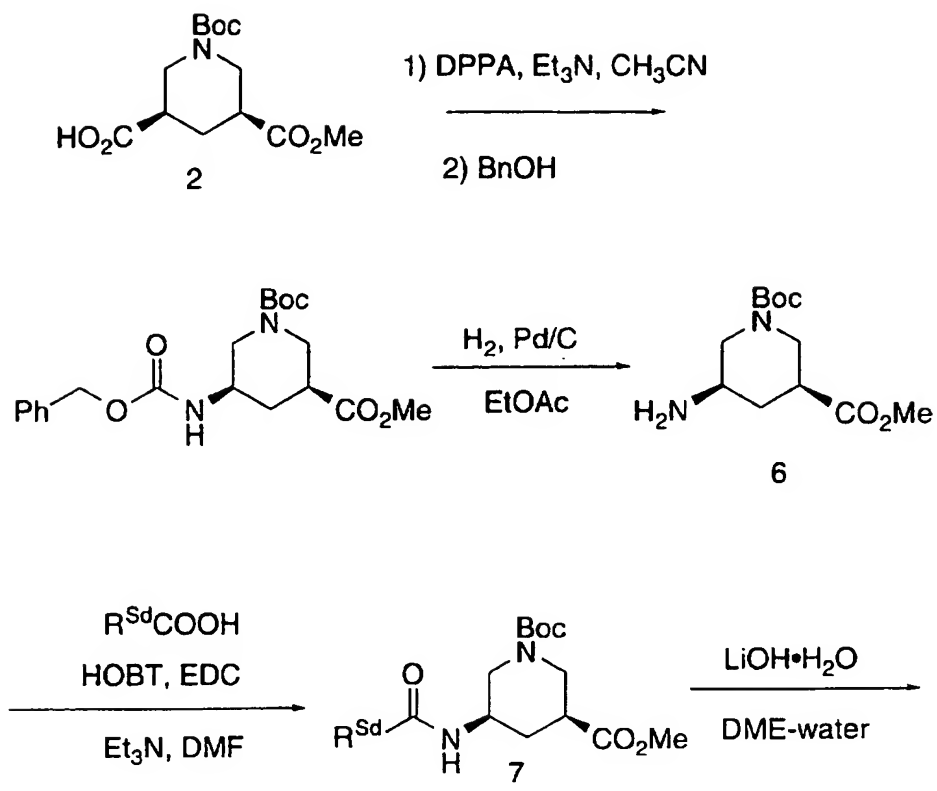
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SCHEME 1

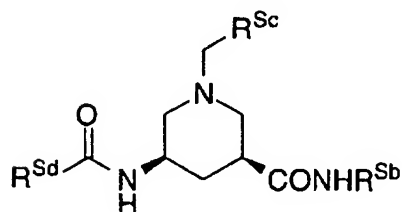
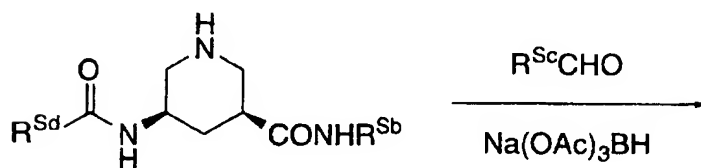
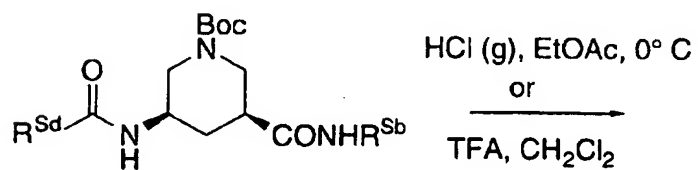
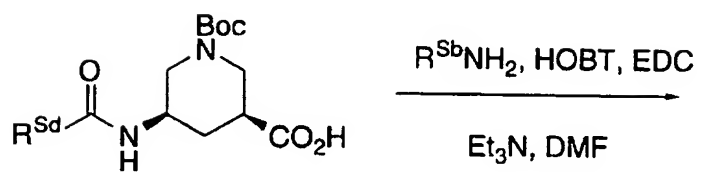
- 62 -

SCHEME 2

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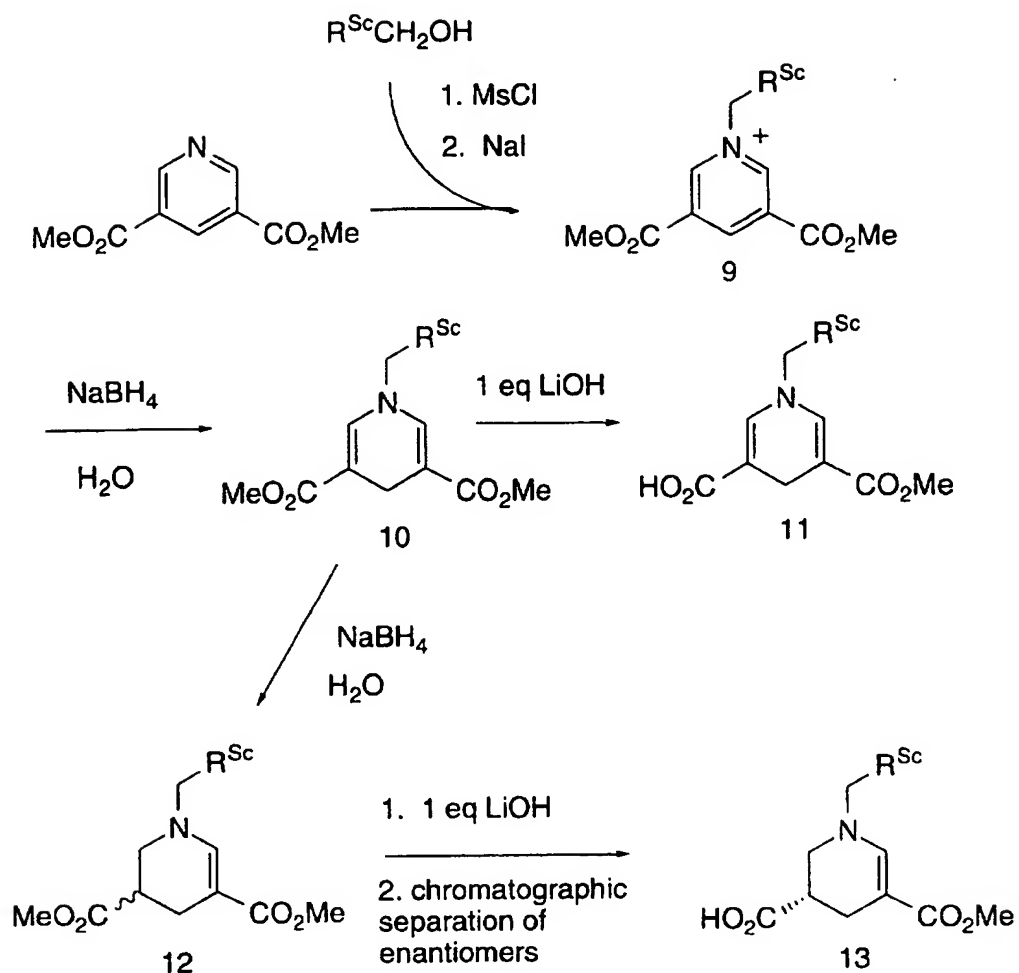
SCHEME 3

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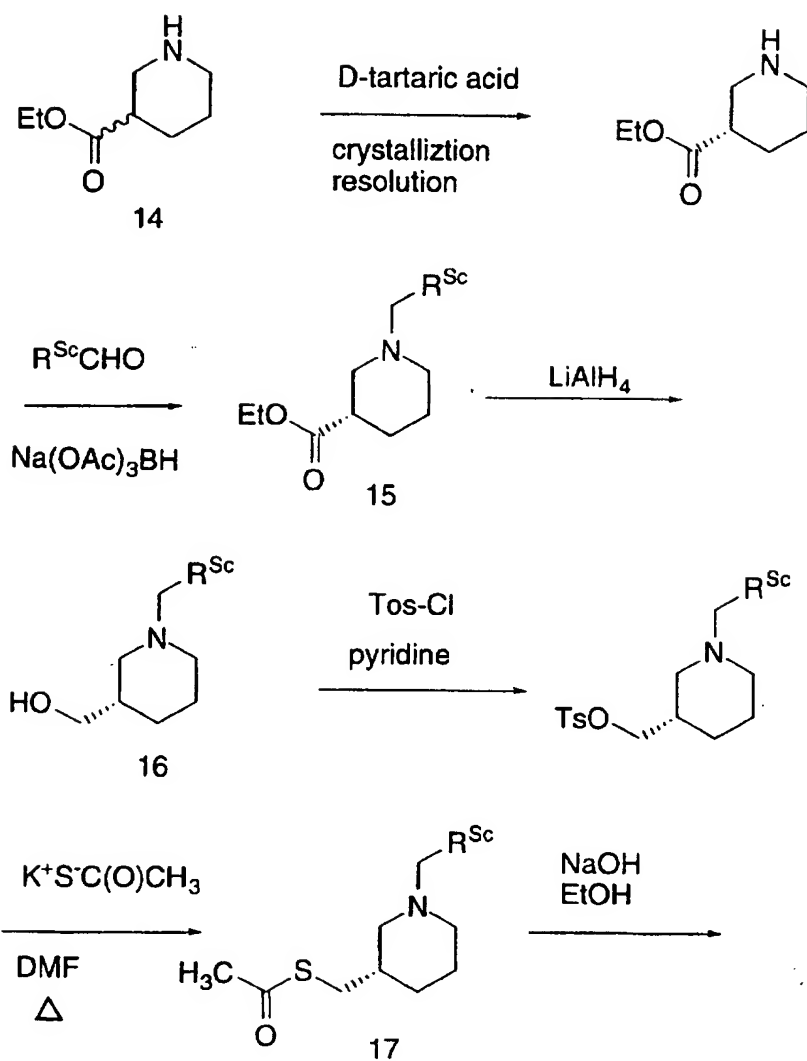
SCHEME 3 (continued)

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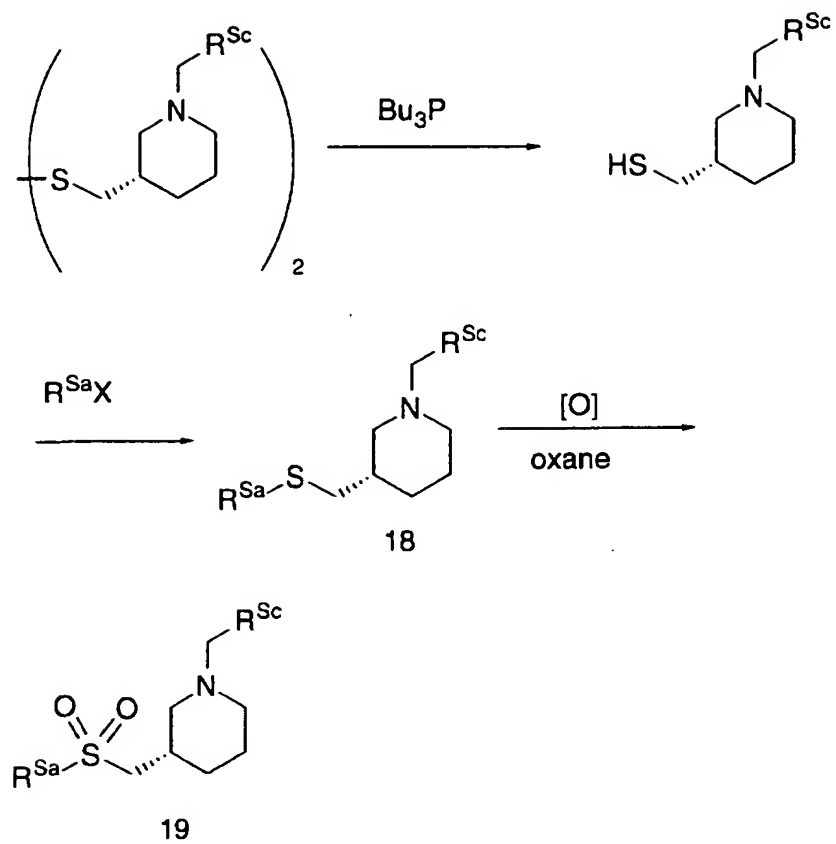
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SCHEME 4

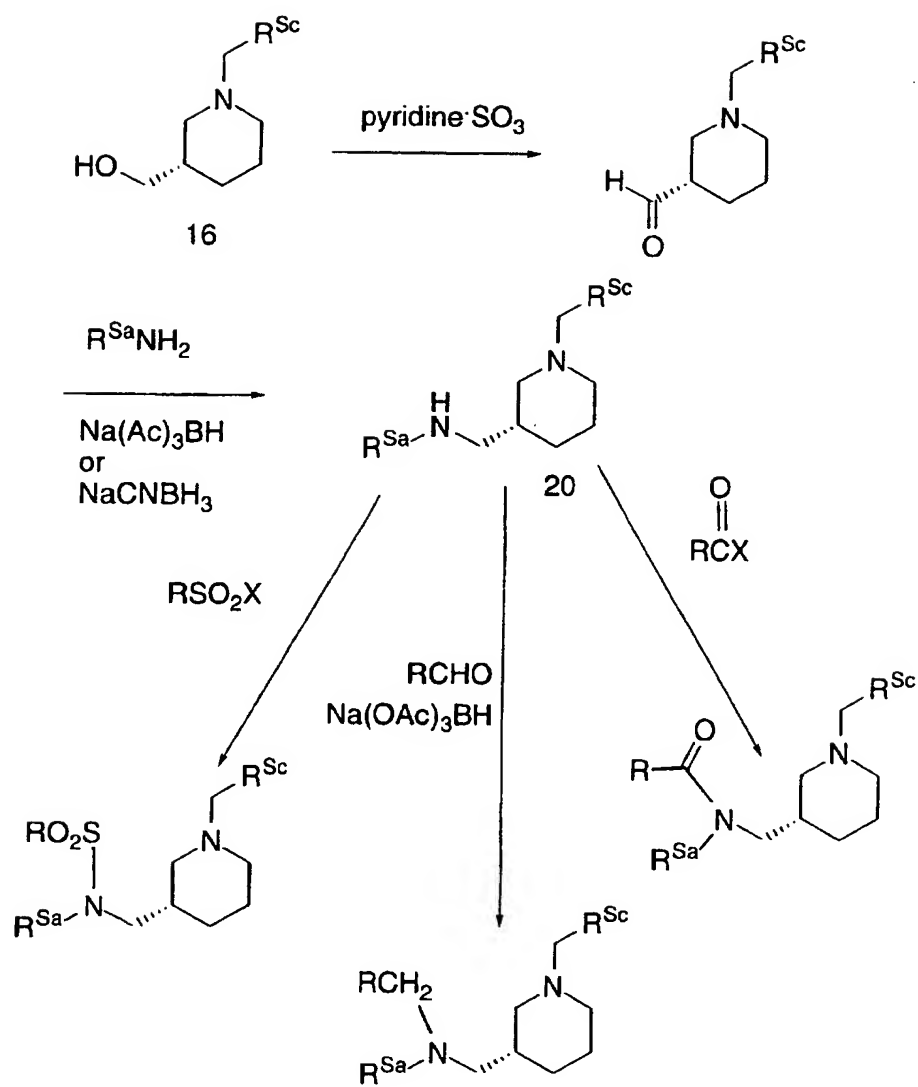
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SCHEME 5

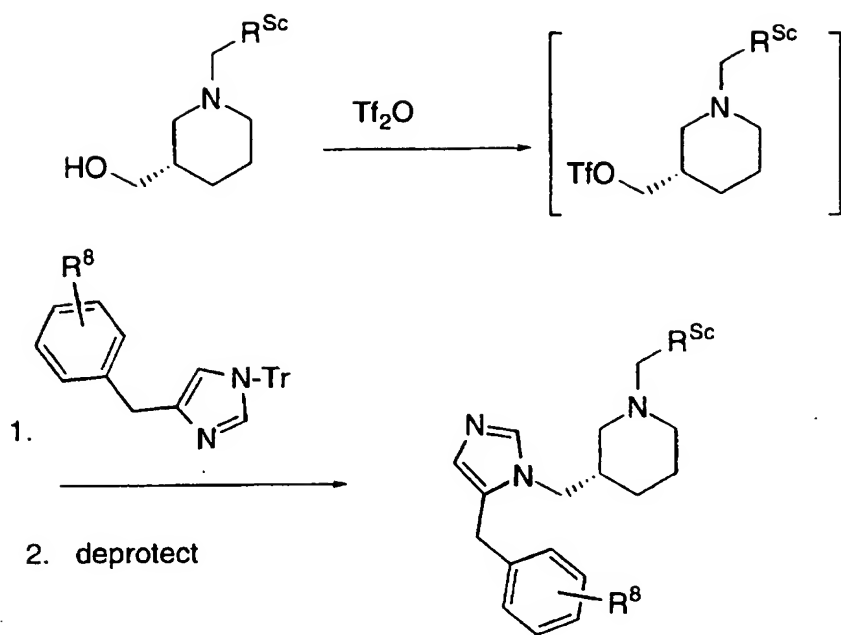
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SCHEME 5 (continued)

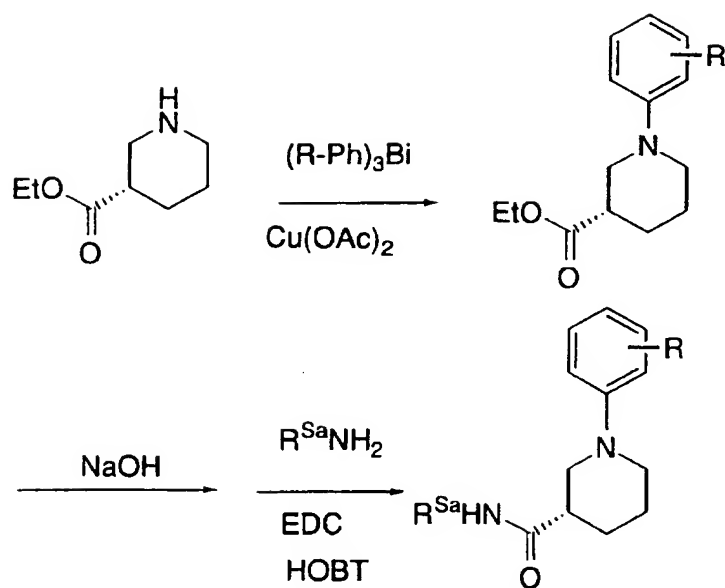
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SCHEME 6

- 69 -

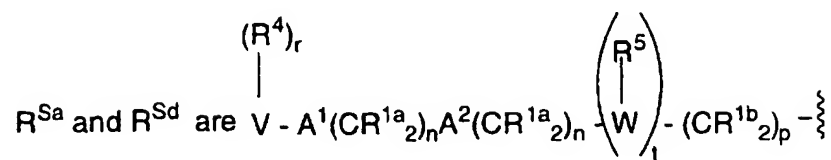
SCHEME 7

- 70 -

SCHEME 8

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In the above Schemes it is understood that



or a protected precursor thereof;

- 5 $R^{Sc}CH_2-$ is R^2 or a protected precursor thereof; and
 $R^{Sb}-$ is R^6 or a protected precursor thereof; and
 $R-$ is a "substituent" or a protected precursor thereof.

10 It is understood that a variety of amines and acids, either commercially available or readily synthesized by reactions well known in the art, which contain the side-chain moieties R^{Sa} and $R^{Sd}(C=O)$ may be utilized in the reactions described hereinabove. Schemes 9-21 illustrate specific reactions wherein such intermediates containing the side-chain moieties R^{Sa} and $R^{Sd}(C=O)$ may be prepared. It is understood that while Schemes 9-21 illustrate preparation of both
 15 protected and unprotected intermediates, a person of ordinary skill would appreciate that subsequent reactions which utilize those intermediates, such as those described in Schemes 1-8, may require protection and eventual deprotection of certain intermediate moieties..

20 The selectively protected intermediate **20** utilized in the synthesis illustrated in Scheme 9 can be reductively alkylated with a variety of aldehydes, such as **21**. The aldehydes can be prepared by standard procedures, such as that described by O. P. Goel, U. Krolls, M. Stier and S. Kesten in Organic Syntheses, **1988**, 67, 69-75. The reductive alkylation can be accomplished at pH 5-7 with a variety of
 25 reducing agents, such as sodium triacetoxyborohydride or sodium cyanoborohydride in a solvent such as dichloroethane, methanol or dimethylformamide. The ester product **22** can be deprotected with trifluoroacetic acid in methylene chloride to give the substituted diamine **23**. That diamine may be isolated in the salt form, for example, as a

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trifluoroacetate, hydrochloride or acetate salt, among others. The product diamine **23** can be further selectively protected and reductively alkylated with a second aldehyde to obtain an analogous tertiary amine. Alternatively, the diamine **23** can be cyclized to obtain intermediates such as the dihydroimidazole **24** by procedures known in the literature. The ester **24** can then be utilized in a reaction such as illustrated in Scheme 3 hereinabove or can be converted to the amine **26**, via the azido intermediate **25**. That amine can then be utilized in reactions such as illustrated in Scheme 1.

Scheme 10 illustrates preparation of aralkyl imidazolyl intermediates **31** that can be utilized in reactions such as illustrated in Scheme 3. Thus imidazole acetic acid **27** can be converted to the protected acetate **29** by standard procedures, and **29** can be first reacted with an alkyl halide, then treated with refluxing methanol to provide the regiospecifically alkylated imidazole acetic acid ester **30**. Hydrolysis provides the acetic acid **31**.

Alternatively, intermediate **31** can be converted into the homologous amine **34** via the azido intermediate **33**, as shown in Scheme 11. This amine can then be utilized in reactions such as illustrated in Scheme 1.

Preparation of amine intermediates having mixed heteroatom substitution is illustrated in Schemes 12 and 13. Thus the protected serine **35** can be reduced to the alcohol **36**, which can then undergo a Mitsunobu reaction to provide the phthalimidyl intermediate **37**. Deprotection and selective reprotection give the alcohol **39**, which can be oxidized to the aldehyde **40**. The aldehyde **40** can be subsequently alkylated and finally deprotected to provide the amine intermediate **41**.

The Boc protected phthalimidyl alcohol **39** can also be utilized to synthesize 2-aziridinylmethyamines such as **42** (Scheme 13). Treating **39** with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide led to the formation of aziridine **42**. The aziridine may then be reacted in the presence of a nucleophile, such

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as a thiol, in the presence of base to yield, after deprotection, the ring-opened intermediate amine **43**.

In addition, amines such as **48** derived from amino acids such as O-alkylated tyrosines can be prepared according to standard procedures as shown in Scheme 14. Illustrated is a procedure where the amine moiety is derived from the azide of an intermediate such as **47**.

Schemes 15-18 illustrate syntheses of suitably substituted alkanols useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. The hydroxyl moiety of such intermediates may be converted into the corresponding amine, as illustrated in Scheme 15 or may be converted to a suitable leaving group, as illustrated in Scheme 17. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

Compounds of the instant invention wherein the $A^1(CR^{1a}_2)_nA^2(CR^{1a}_2)_n$ linker is a substituted methylene may be synthesized by the methods shown in Scheme 19. Thus, the N'-protected imidazolyl iodide **50** is reacted, under Grignard conditions with a suitably protected benzaldehyde to provide the alcohol **51**. Acylation, followed by the alkylation procedure illustrated in the Schemes above (in particular, Scheme 7) provides the instant compound **52**. If other R^1 substituents are desired, the acetyl moiety can be manipulated as illustrated in the Scheme.

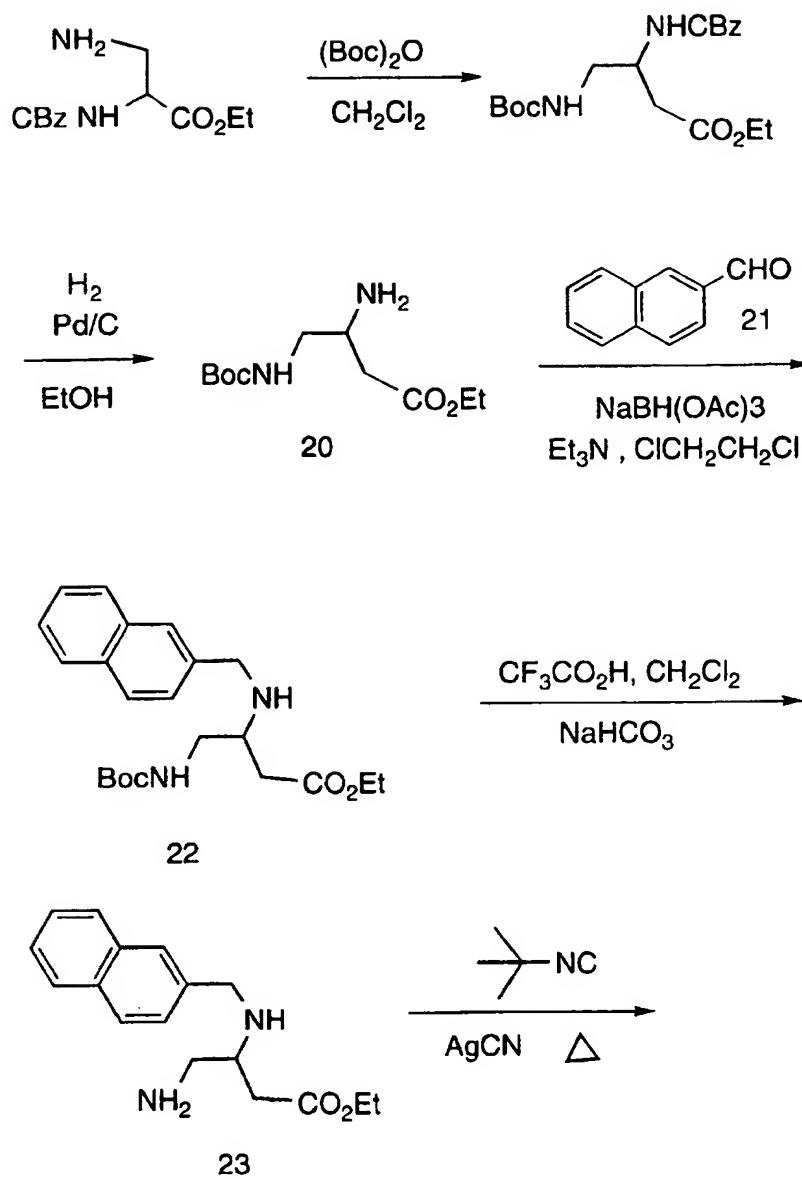
Scheme 20 illustrates synthesis of an instant compound wherein a non-hydrogen R^{5b} is incorporated in the instant compound. Thus, a readily available 4-substituted imidazole **53** may be selectively iodinated to provide the 5-iodoimidazole **54**. That imidazole may then be protected and coupled to a suitably substituted benzyl moiety to provide intermediate **55**. Intermediate **55** can then undergo the alkylation reactions that were described hereinabove.

Compounds of the instant invention wherein the $A^1(CR^{1_2})_nA^2(CR^{1_2})_n$ linker is oxygen may be synthesized by methods known in the art, for example as shown in Scheme 21. The suitably substituted phenol **56** may be reacted with methyl N-

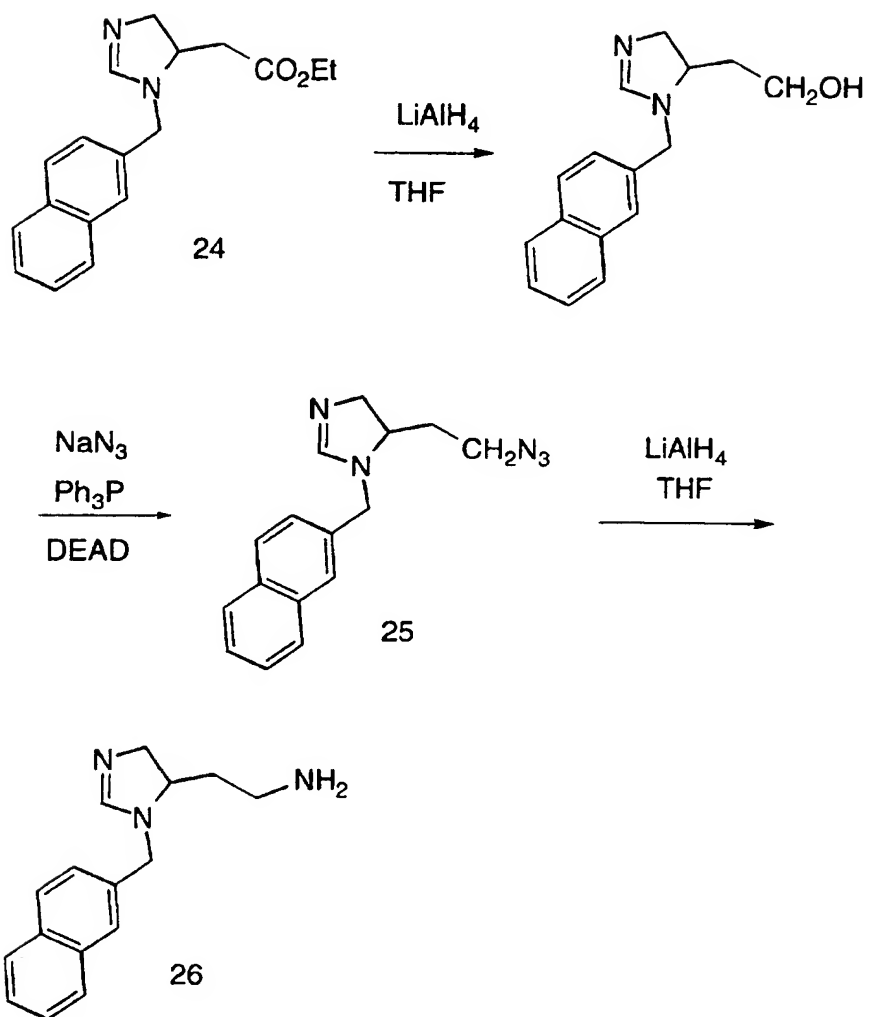
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(cyano)methanimidate to provide the 4-phenoxyimidazole **57**. After selective protection of one of the imidazolyl nitrogens, the intermediate **58** can undergo alkylation reactions as described for the benzylimidazoles hereinabove.

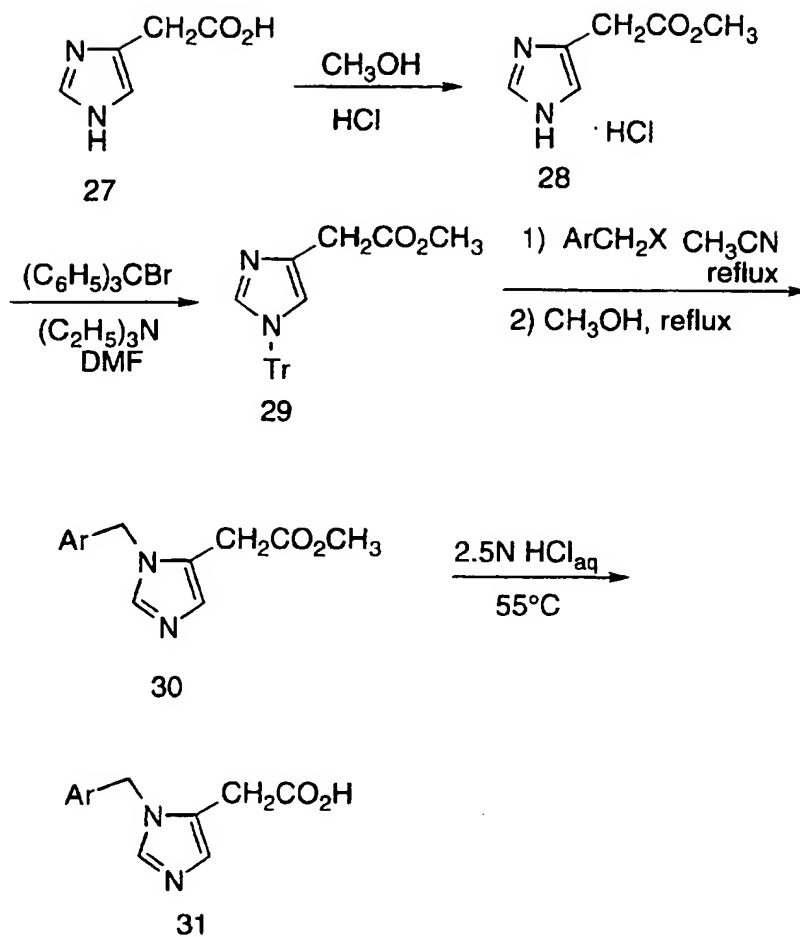
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SCHEME 9

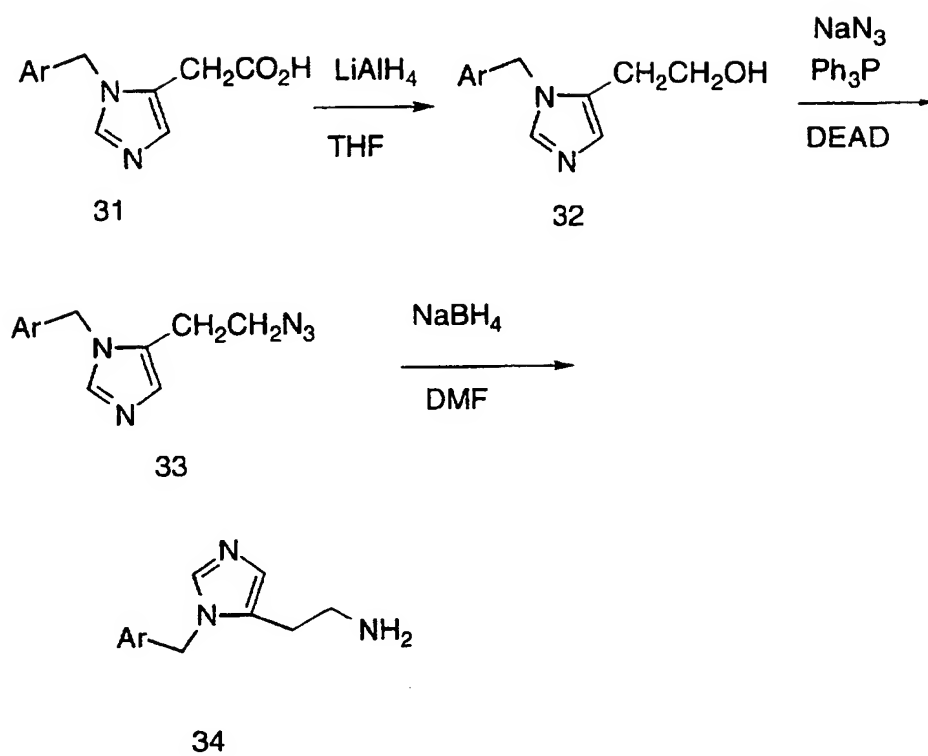
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SCHEME 9 (continued)

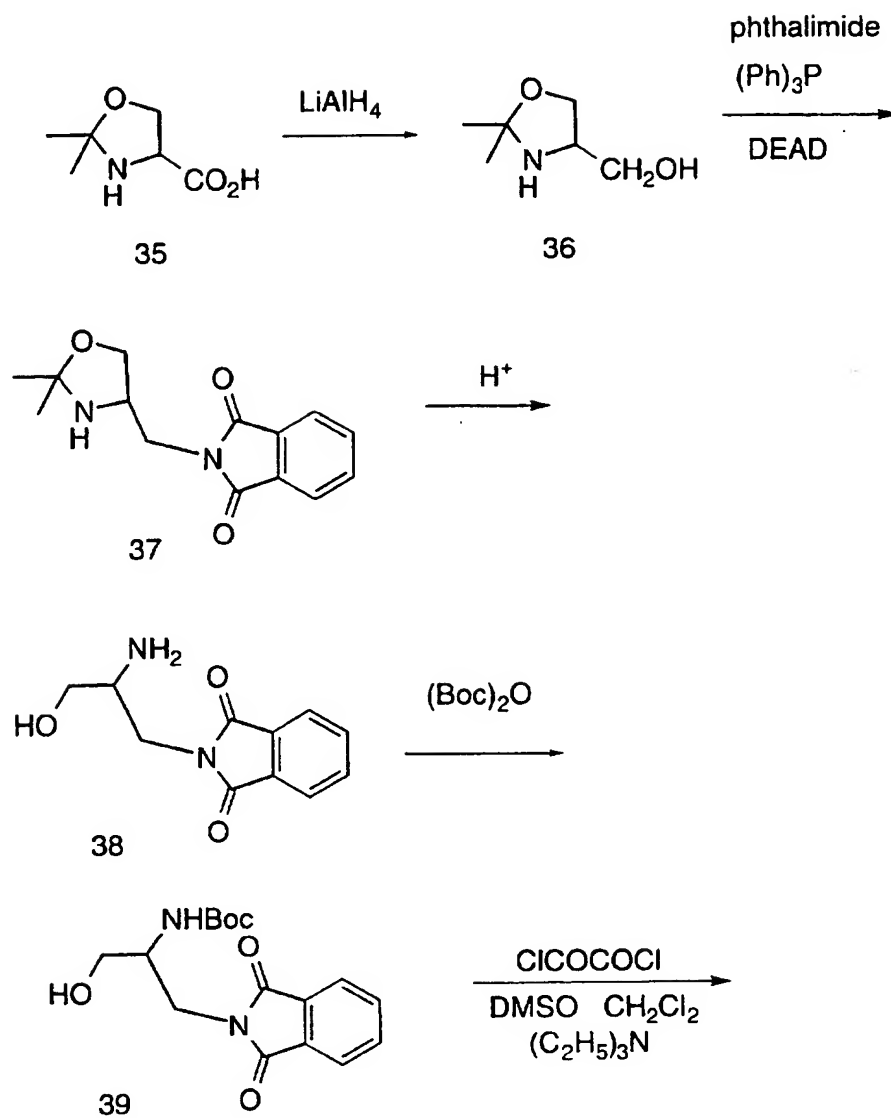
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SCHEME 10

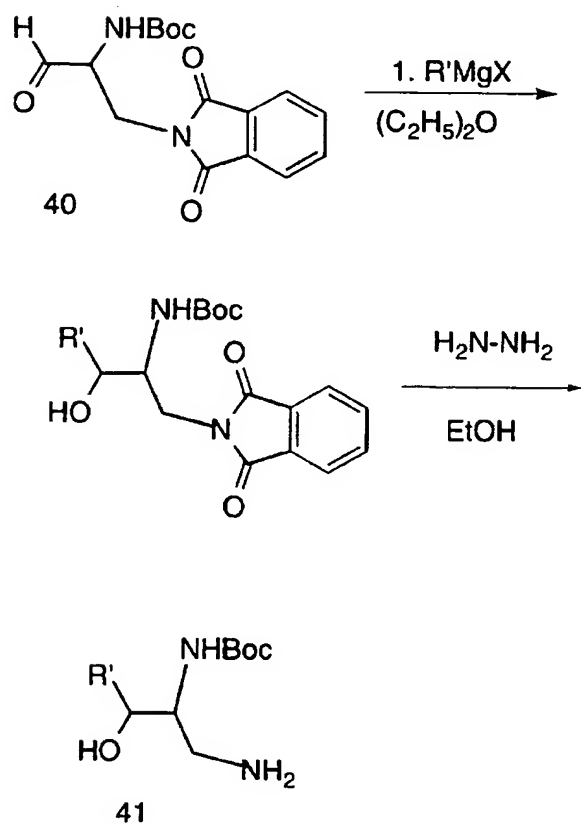
- 78 -

SCHEME 11

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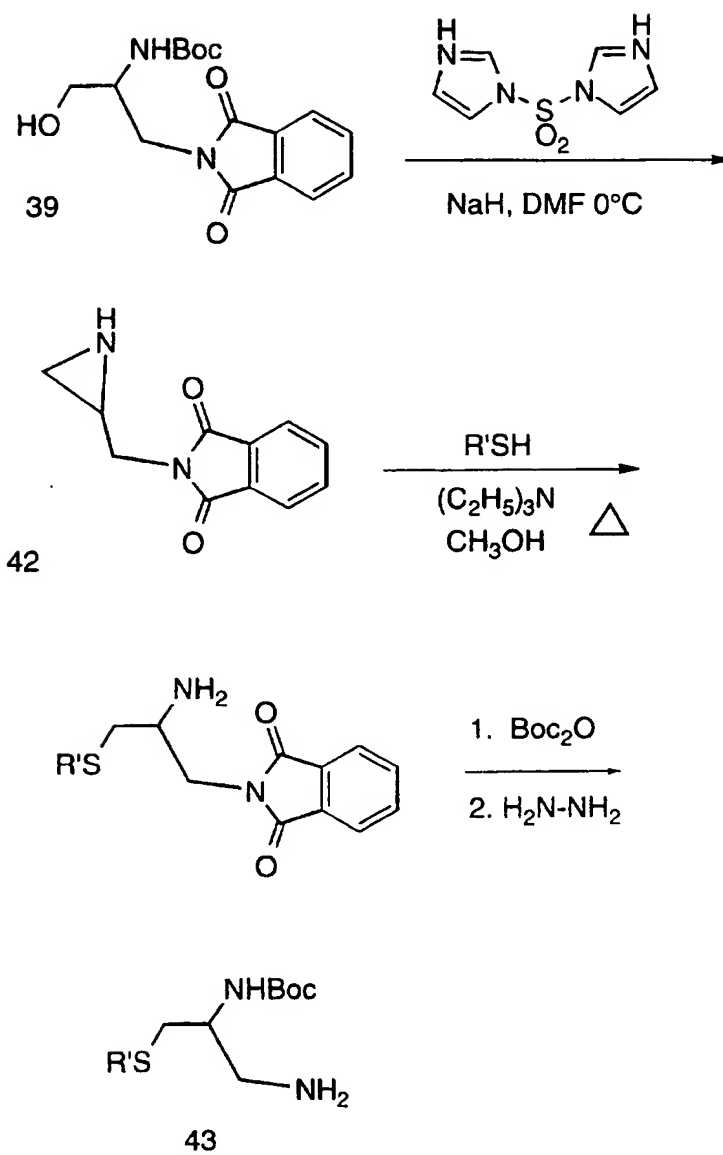
SCHEME 12

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SCHEME 12 (continued)

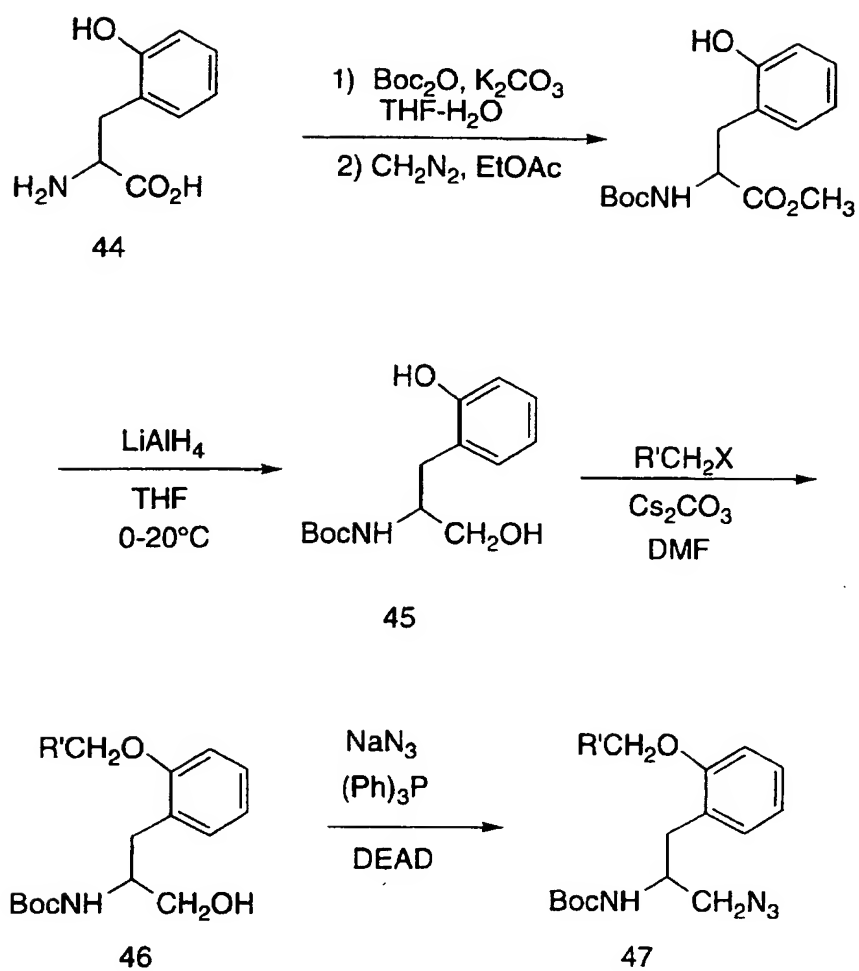
wherein R' is R^{1a} or a protected precursor thereof

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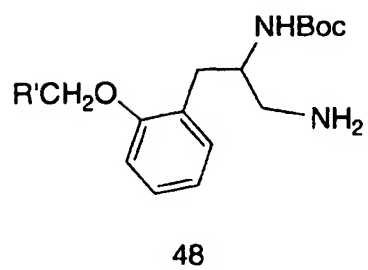
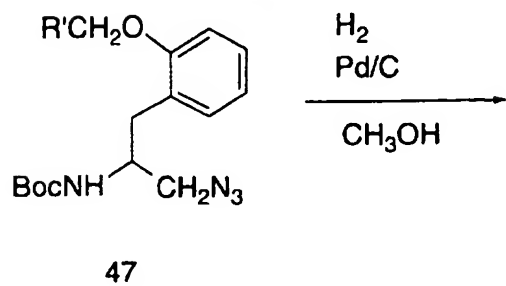
SCHEME 13

wherein R' is $(\text{R}^4)_r\text{-V-}$ or a protected precursor thereof

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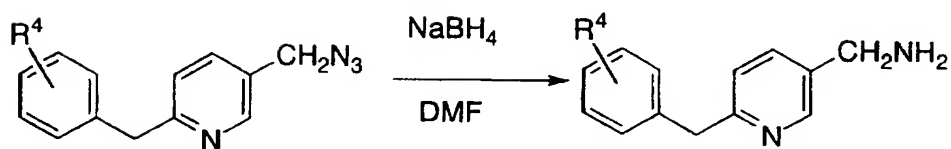
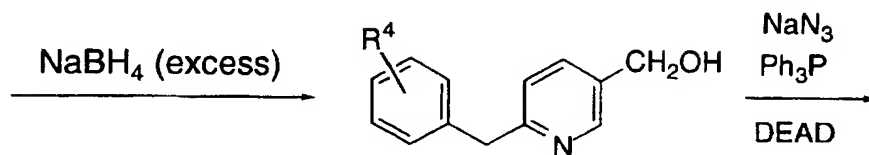
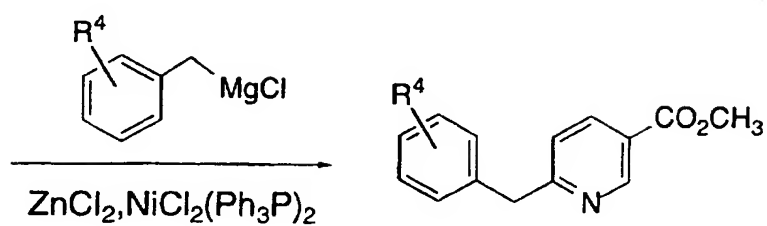
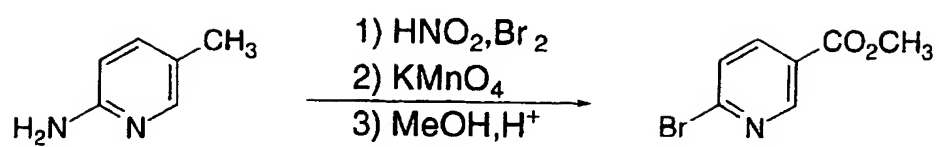
SCHEME 14

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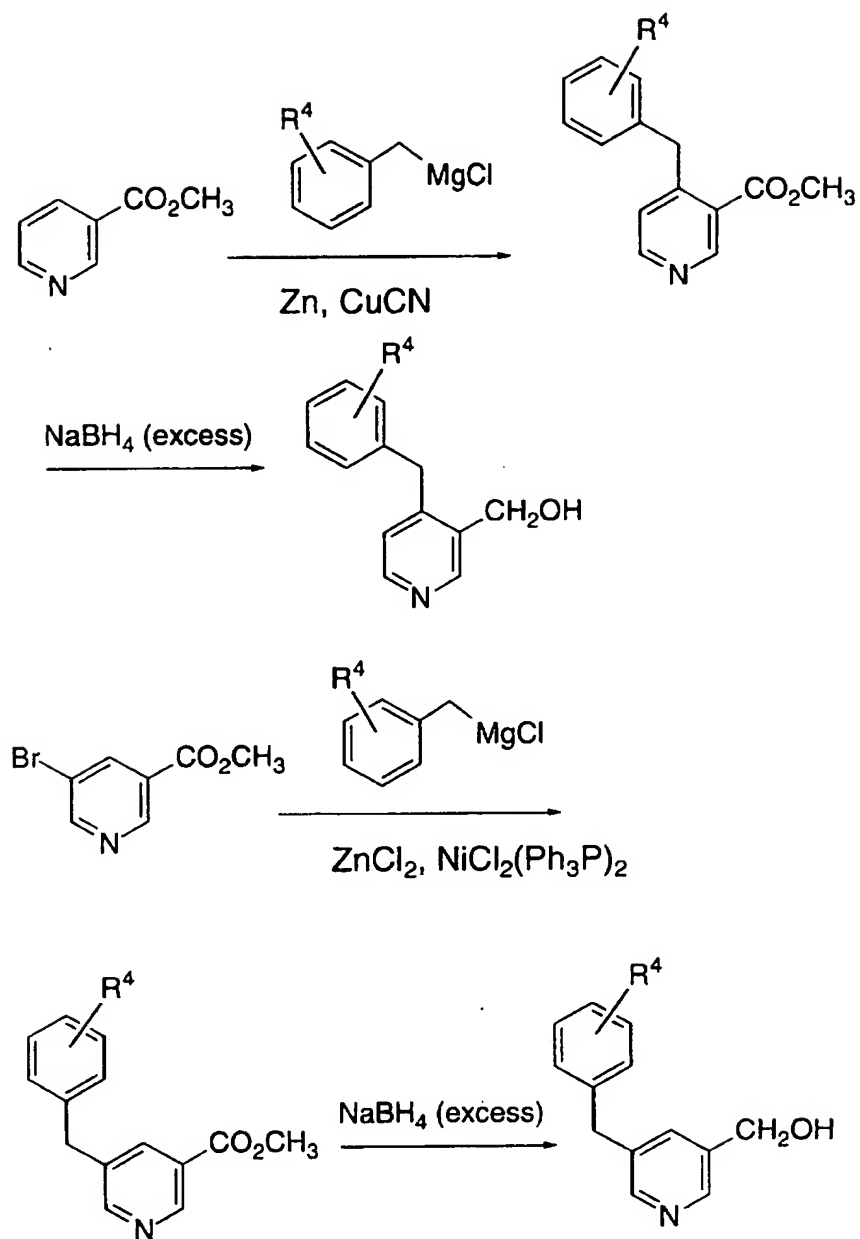
SCHEME 14 (continued)

wherein $R'CH_2-$ is R^8 or a protected precursor thereof

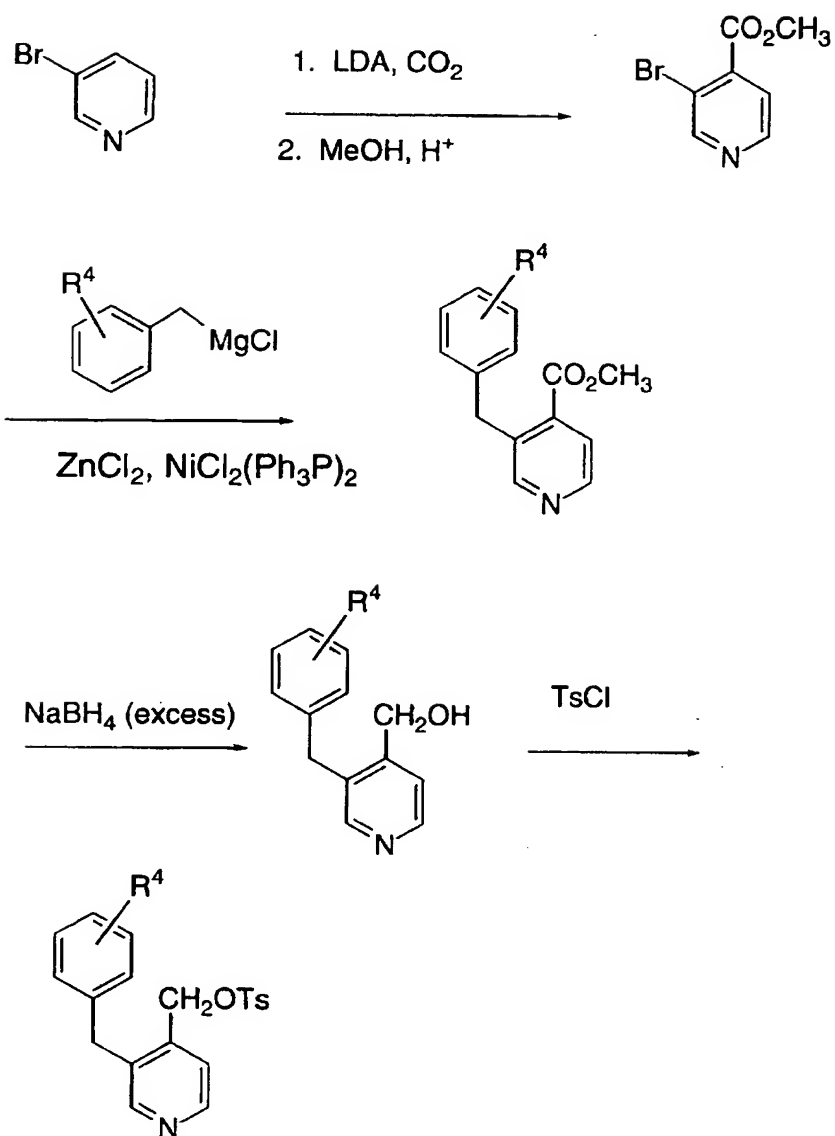
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SCHEME 15

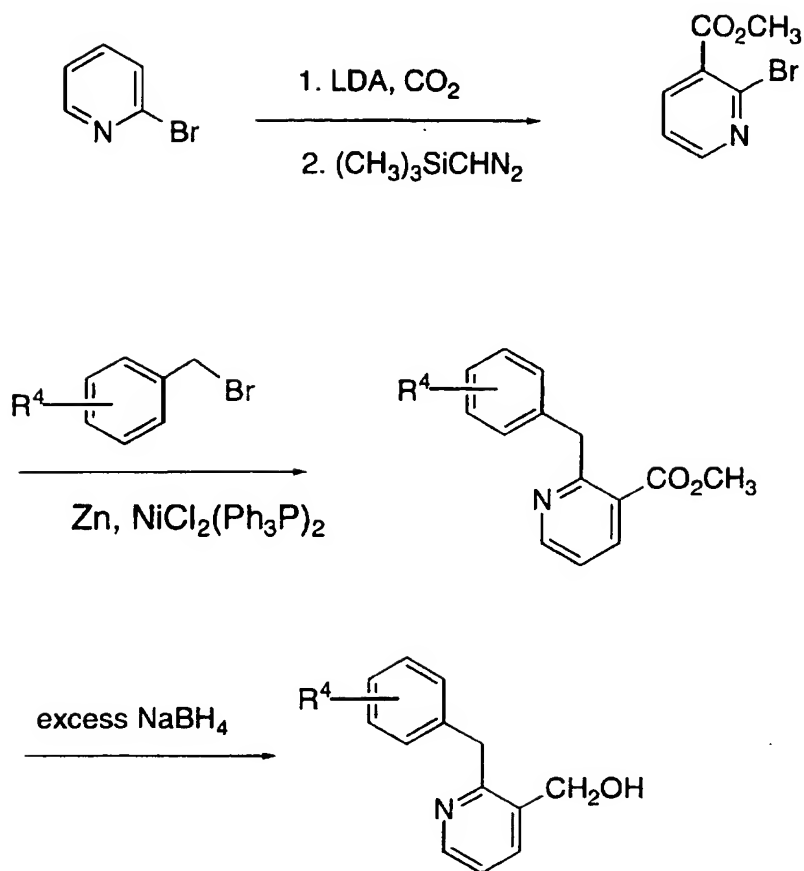
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SCHEME 16

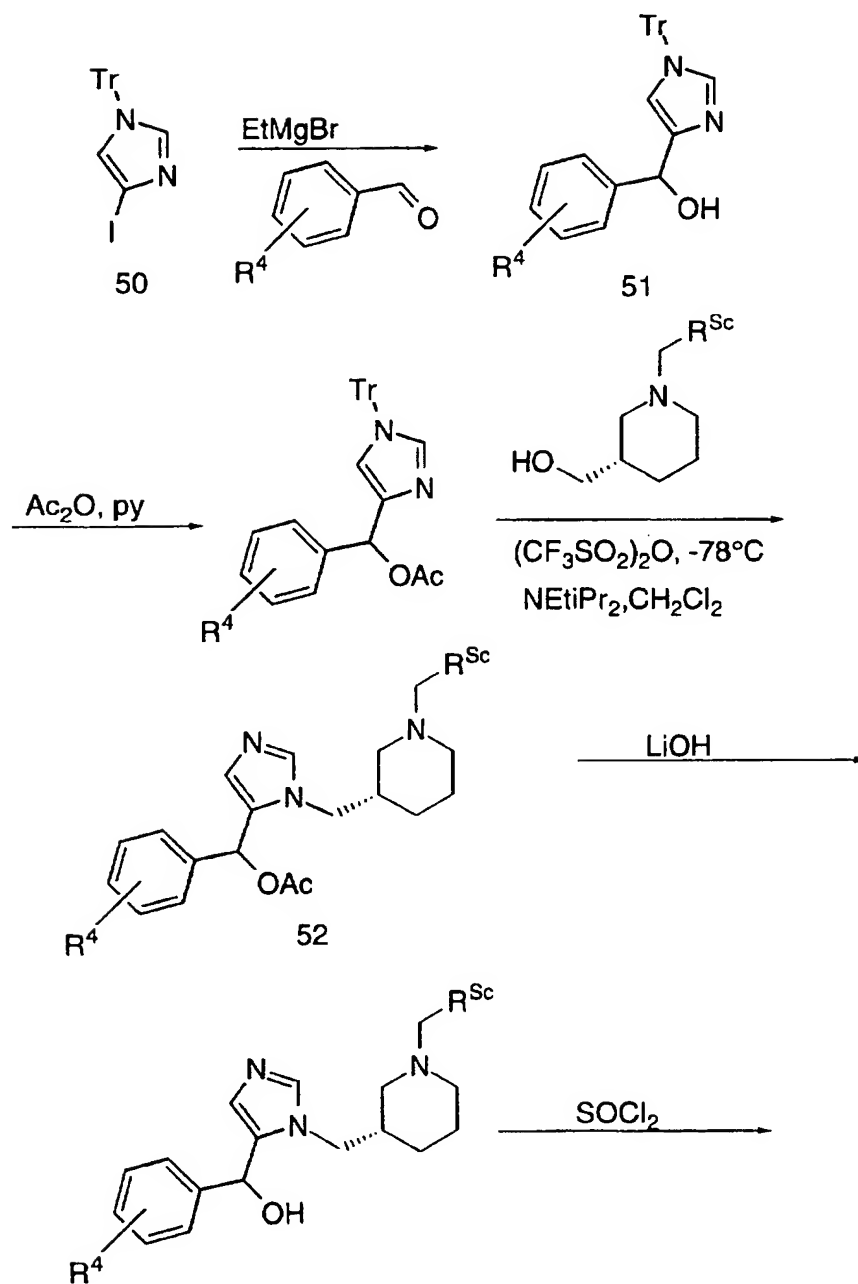
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SCHEME 17

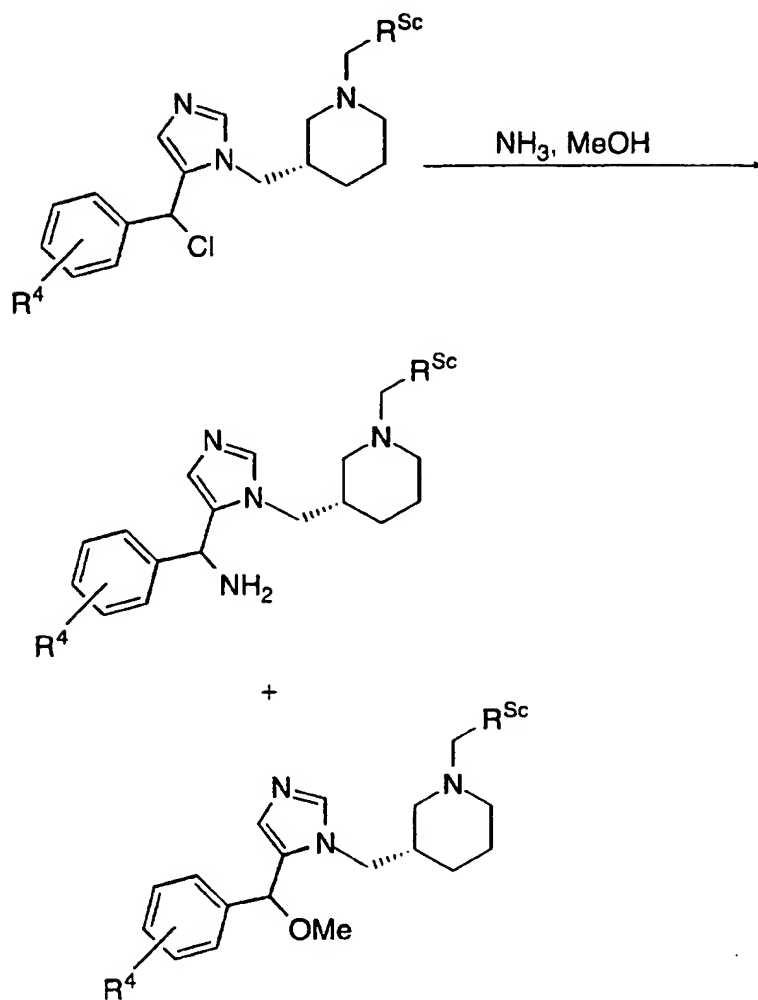
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SCHEME 18

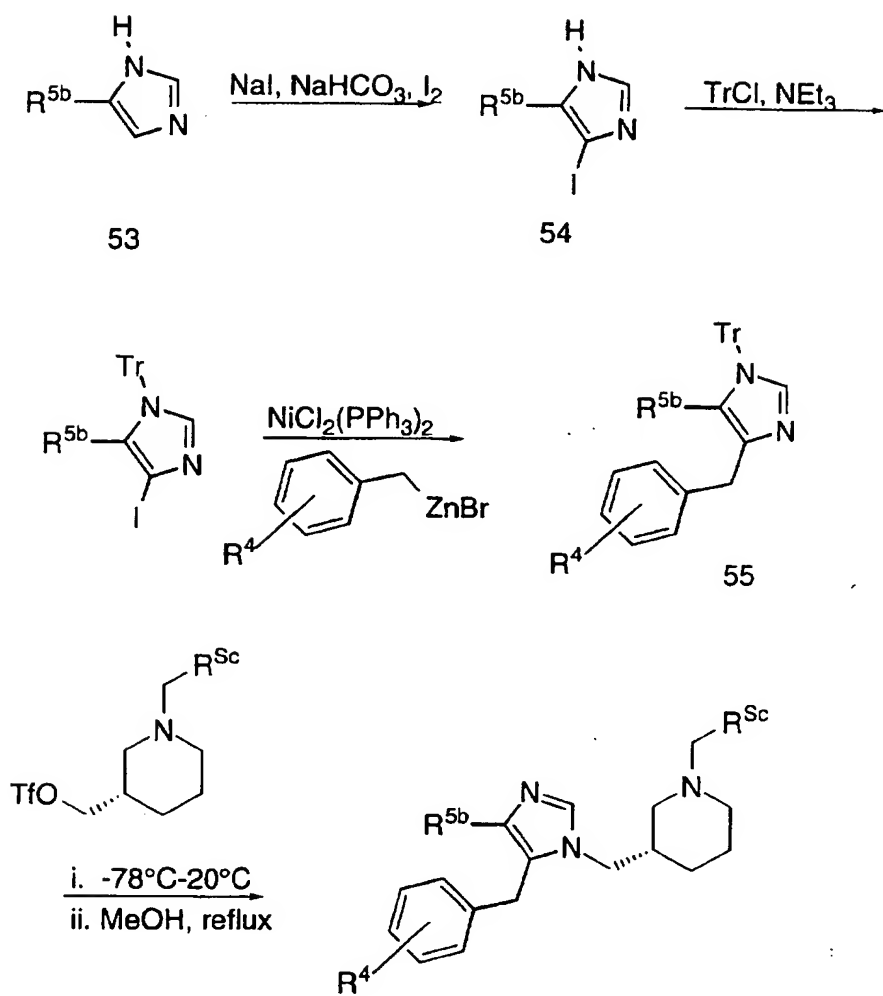
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SCHEME 19

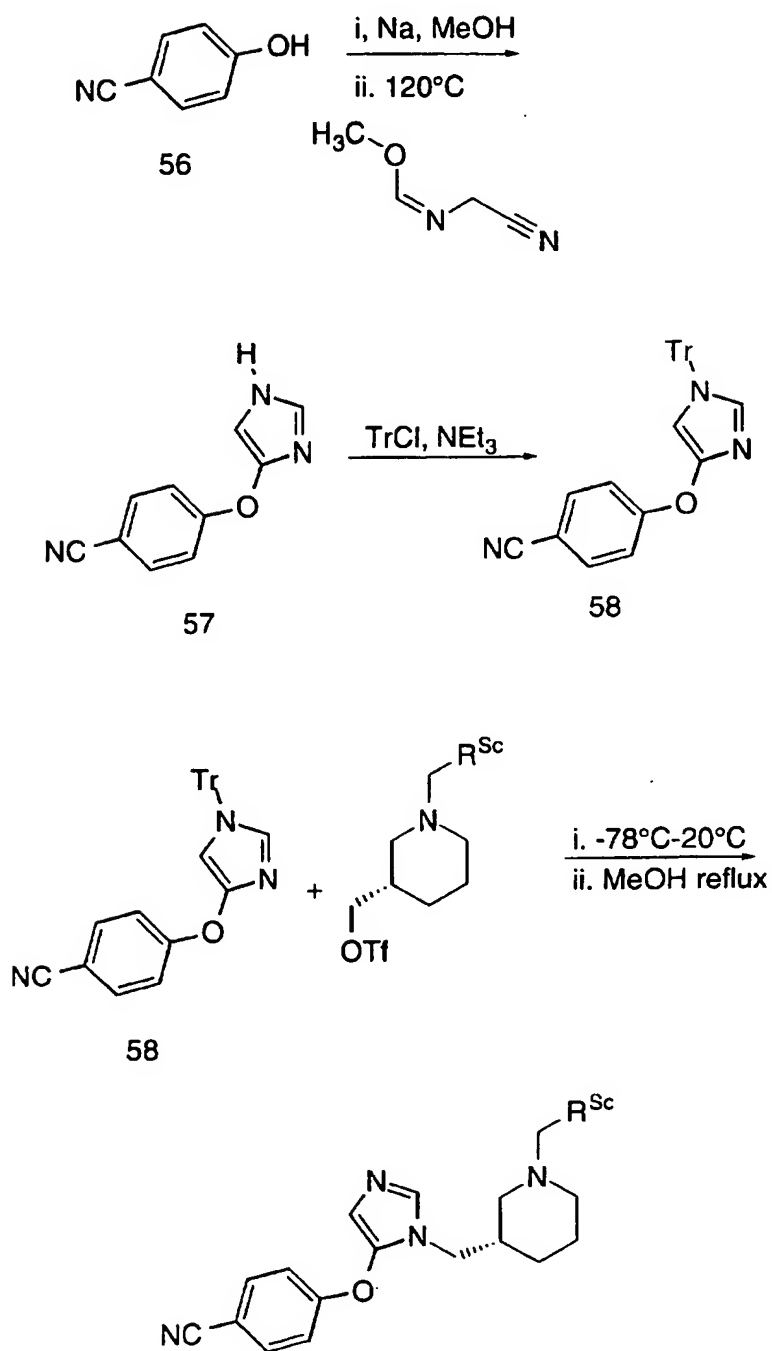
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SCHEME 19 (continued)

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SCHEME 20

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SCHEME 21

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The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras activity (i.e., neurofibromin (NF-1), neu, scr, abl, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenesis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenesis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992)).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature medicine*, 1:541-545(1995)).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

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American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al. *FASEB Journal*, 2:A3160 (1988)).

The instant compounds may also be useful for the treatment of fungal infections.

5 The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The
10 compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

 For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for
15 example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral
20 administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the
25 pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

 The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the
30 administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The

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solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specific amounts, as well as any product which results, directly or indirectly, from combination of the specific ingredients in the specified amounts.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the

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assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a K_i substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

20

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof. Purification by HPLC or column chromatography was utilized for each of the Examples 1-24 as set forth below.

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EXAMPLE 1

Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5

Step A: Preparation of Pyridine-3,5-dicarboxylic acid methyl ester hydrochloride

Pyridine-3,5-dicarboxylic acid (5.00 g, 29.9 mmol) was stirred in CH₃OH (100 mL), cooled in an ice bath, and treated dropwise with thionyl chloride (17.45 mL, 239.2 mmol). After 0.5 hr, the reaction mixture was refluxed for 48 hrs. Concentration to dryness gave the title compound as an off-white solid.

10

Step B: Preparation of Piperidine-*cis, trans*-3,5-dicarboxylic acid methyl ester hydrochloride

15

Pyridine-3,5-dicarboxylic acid methyl ester hydrochloride (7.07 g, 30.5 mmol) was dissolved in acetic acid (75 mL), treated with platinum(IV) oxide (100 mg, 0.44 mmol) and shaken on a Parr apparatus at 50 psi overnight. The reaction mixture was filtered through celite and concentrated to dryness to give the title compound.

20

Step C: Preparation of 1-(t-Butoxycarbonyl)piperidine-*cis* and *trans*-3,5-dicarboxylic acid methyl ester

Piperidine-3,5-dicarboxylic acid methyl ester hydrochloride (7.11 g, 29.9 mmol) was dissolved in THF (60 mL) and H₂O (60 mL). Sodium bicarbonate (13.81 g, 0.164 mol) was added followed by di-*tert*-butyl dicarbonate (9.79 g, 44.9 mmol). The mixture was stirred at ambient temperature for 5 hrs. The THF was removed under reduced pressure, and the solution was extracted with CH₂Cl₂ (3x100 mL). The combined CH₂Cl₂ layers were washed with brine and dried (MgSO₄). Filtration and concentration to dryness gave,

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after chromatography (silica gel, 10% ethyl acetate/hexane), racemic 1-(t-Butoxycarbonyl)piperidine-*cis*-3,5-dicarboxylic acid methyl ester and racemic 1-(t-Butoxycarbonyl)piperidine-*trans*-3,5-dicarboxylic acid methyl ester.

5

Step D: Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-piperidine-5-carboxylic acid

1-(t-Butoxycarbonyl)piperidine-*cis*-3,5-dicarboxylic acid methyl ester (0.761 g, 2.52 mmol) was dissolved in DME (6 mL) and H₂O (6 mL) followed by addition of LiOH·H₂O (0.106 g, 2.52 mmol). The mixture was stirred at ambient temperature overnight. The DME was removed under reduced pressure, taken up in EtOAc and water, acidified to pH 3, and extracted with EtOAc (10X). The EtOAc layers were combined, dried (MgSO₄), filtered, and concentrated to dryness to give the title compound after chromatography (silica gel, 1-3% MeOH/CH₂Cl₂).

Step E: Preparation of 3-(4-cyanobenzyl) histamine
N^Y-Pivaloyloxymethyl-N^α-phthaloylhistamine (4.55 g, 12.8 mmol) was prepared as previously described (J. C. Emmett, F. H. Holloway, and J. L. Turner, *J. Chem. Soc., Perkin Trans. 1*, 1341, (1979)). α-Bromo-p-tolunitrile (3.77 g, 19.2 mmol) was dissolved in acetonitrile (70 mL). The solution was heated at 55°C for 4 h, cooled to room temperature, and filtered to remove the white solid. The acetonitrile (30 mL) was concentrated to 1/2 its volume under reduced pressure and the solution was heated at 55°C overnight. The solution was cooled and filtered to give a white solid. The volume of the filtrate was reduced to 10 mL, the solution was heated at 55°C for 1 hr, then cooled to room temperature, diluted with EtOAc (25 mL) and filtered to obtain additional white solid. The solids were combined, dried, and used without further purification.

1-Pivaloyloxymethyl-3-(4-cyanobenzyl)-4-(2-phthalimidoethyl)imidazolium bromide (6.13 g, 11.1 mmol) in methanol (100 mL) was saturated with ammonia gas while the

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temperature was maintained below 30°C. The solution was stirred for 1 hr, concentrated to dryness, and extracted with CH₂Cl₂ (3x200 mL), dried (MgSO₄), concentrated, and chromatographed (silica gel, 10:90:1 MeOH/CH₂Cl₂/NH₄OH) to give 4-cyanobenzyl-N α -phthaloylhistamine.

5 3-(4-Cyanobenzyl)-N α -phthaloylhistamine (1.64 g, 4.61 mmol), and hydrazine (1.46 mL, 46.1 mmol) were dissolved in absolute EtOH (70 mL). The solution was concentrated after 1 hr and filtered to remove a white precipitate which was washed several times with EtOH. The filtrate was concentrated and the residue was chromatographed
10 (silica gel, 10:90:1 MeOH/CH₂Cl₂/NH₄OH) to give the title compound.

Step F: Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbonyl]-piperidine

15 1-t-Butoxycarbonyl-*cis*-3-methoxycarbonyl-piperidine-5-carboxylic acid (1.45 g, 5.06 mmol), 3-(4-cyanobenzyl) histamine (1.14 g, 5.06 mmol), HOBT (0.72 g, 5.31 mmol), EDC (1.02 g, 5.31 mmol), Et₃N (0.63 mL, 4.55 mmol) were dissolved in DMF (20 mL). The solution was stirred overnight, concentrated, and partitioned between
20 EtOAc (300 mL) and sat NaHCO₃ solution (200 mL). The organics were washed with brine, dried (MgSO₄), filtered and concentration to dryness gave the title compound after chromatography (silica gel, 1-2% MeOH/CHCl₃). ¹H NMR (CDCl₃); δ 7.64 (d, 2H, J=8 Hz), 7.52 (s, 1H), 7.14 (d, 2H, J=8 Hz), 6.90 (s, 1H), 6.12 (br s, 1H), 5.21 (s, 2H),
25 4.10-4.33 (m, 2H), 3.69 (s, 3H), 3.32-3.46 (m, 2H), 2.71-2.92 (m, 2H), 2.54-2.68 (m, 2H) 2.39-2.50 (m, 1H), 2.12-2.28 (m, 2H), 1.78-1.92 (m, 1H), 1.45 (s, 9H). FAB MS 496 (M+1)
Anal. calcd for C₂₆H₃₃N₅O₅•0.3 H₂O: C, 62.34; H, 6.76; N, 13.98;
Found: C, 62.32; H, 6.61; N, 13.89.

30

Following the procedure of Steps D-F but substituting the 1-(t-butoxycarbonyl)piperidine-*trans*-3,5-dicarboxylic acid methyl ester prepared as described in Step C for the 1-(t-Butoxycarbonyl)piperidine-*cis*-3,5-dicarboxylic acid methyl ester utilized in Step D provided 1-(t-

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butoxycarbonyl)-*trans*-3-methoxy-carbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]-piperidine.

EXAMPLE 2

5

Preparation of 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbonyl] piperidine

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Step A: Preparation of *cis*-3-Methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (1.14 g, 2.30 mmol) was dissolved in CH₂Cl₂ (12 mL). Trifluoroacetic acid (6 mL) was added and the solution was stirred at ambient temperature for 3 h. The solution was concentrated to dryness to give the title compound.

20

Step B: Preparation of 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
cis-3-Methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (59.0 mg, 0.149 mmol) was dissolved in MeOH (2 mL). Phenylacetaldehyde (52.3 μ L, 0.447 mmol) was added followed by sodium cyanoborohydride (28.1 mg, 0.447 mmol). The solution was stirred overnight at ambient temperature. The MeOH was removed under reduced pressure and chromatography (silica gel, 1-2% MeOH/CH₂Cl₂/NH₄OH) gave the title compound as a white solid. ¹H NMR (CDCl₃); δ 7.62 (d, 2H, J=8 Hz), 7.50 (s, 1H), 7.08-7.37 (m, 7H), 6.88 (s, 1H), 6.46 (br s, 1H), 5.22 (s, 2H), 3.64 (s, 3H), 3.27-3.19 (m, 1H), 3.03-3.20 (m, 1H), 2.86-3.00 (m, 1H), 2.73-2.85 (m, 3H), 2.44-2.70 (m, 5H), 2.26-2.41 (m, 2H), 1.98-2.10 (m, 2H), 1.80-1.95 (m, 1H). FAB MS 500 (M+1)

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Using the methods described in Example 2, but substituting the requisite aldehyde for phenylacetaldehyde in Step B, the following compounds were prepared:

- 5 1-(1-Naphthylmethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 536 (M + 1)
- 10 1-Benzyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 486 (M + 1)
- 15 1-Methyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 410 (M + 1)
- 20 1-(2-Indanyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 512 (M + 1)
Anal. calcd for C₃₀H₃₃N₅O₃•0.15 H₂O • 0.5 CHCl₃:
C, 63.82; H, 5.94; N, 12.20;
Found: C, 63.83; H, 5.95; N, 12.16.
- 25 1-(2,2-Diphenylethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 576 (M + 1)
Anal. calcd for C₃₅H₃₇N₅O₃•0.9 H₂O: C, 71.02; H, 6.61; N, 11.83;
Found: C, 71.08; H, 6.35; N, 11.71.
- 30 Separation of the diastereomers of this compound on a Chiralcel OD HPLC column eluting with hexane/0.2% DEA: 1-propanol, 55:45 provided the following:
1-(2,2-Diphenylethyl)-*cis*-3(S)-methoxycarbonyl-5-(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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FAB MS 576 (M + 1)

Anal. calcd for C₃₅H₃₇N₅O₃•0.9 H₂O: C, 71.02; H, 6.61; N, 11.83;

Found: C, 71.08; H, 6.35; N, 11.71.

- 5 1-(2,2-Diphenylethyl)-*cis*-3-(R)-methoxycarbonyl-5-(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyle] piperidine

FAB MS 576 (M + 1)

Anal. calcd for C₃₅H₃₇N₅O₃•0.9 H₂O: C, 71.02; H, 6.61; N, 11.83;

Found: C, 71.08; H, 6.35; N, 11.71.

10

1-(3-Phenylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyle] piperidine

FAB MS 514 (M + 1)

- 15 Anal. calcd for C₃₀H₃₅N₅O₃•0.8 H₂O: C, 68.24; H, 6.99; N, 13.26;

Found: C, 68.20; H, 6.69; N, 13.14.

1-(2-Methylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyle] piperidine

- 20 FAB MS 452 (M + 1)

Anal. calcd for C₂₅H₃₃N₅O₃•0.75 H₂O: C, 64.57; H, 7.48; N, 15.06;

Found: C, 64.61; H, 7.19; N, 14.68.

EXAMPLE 3

25

Preparation of 1-Phenethyl-*cis*-3-carboxyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyle] piperidine

- 30 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyle] piperidine (43.1 mg, 0.086 mmol) was dissolved in THF (4 mL) and H₂O (1 mL). A 1N solution of LiOH•H₂O (86.2 uL, 0.086 mmol) was added and the solution was stirred overnight at ambient temperature. The solution was purified on a WATERS PrepPak column (0.1% TFA in CH₃CN: 0.1% TFA in H₂O, 5:95 to 95:5 gradient) to give the title compound.

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- ¹H NMR (CD₃OD) δ 8.72 (s, 1H), 7.78 (d, 2H, J=8 Hz), 7.43 (d, 2H, J=8 Hz), 7.20-7.40 (m, 6H), 5.55 (s, 2H), 3.75 (d, 1H, J=11 Hz), 3.58 (d, 1H, J=11 Hz), 3.30-3.46 (m, 3H), 2.83-3.16 (m, 6H), 2.77 (t, 2H, J=7 Hz), 2.30 (d, 1H, J=13 Hz), 1.65-1.80 (m, 1H), 1.37 (d, 1H, J=6 Hz).
- 5 FAB MS 486 (M+1).

EXAMPLE 4

- Preparation of 1-Phenethyl-*cis*-3-[N-(1-morpholinyl)carbamoyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine
- 10

- The lithium salt of 1-phenethyl-*cis*-3-carboxy-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (55.2 mg, 0.112 mmol), morpholine (11.7 μL, 0.134 mmol), HOOBT (21.9 mg, 0.134 mmol), EDC (25.8 mg, 0.134 mmol), and Et₃N (14.0 μL, 0.101 mmol) were dissolved in DMF (2 mL). The solution was stirred overnight at ambient temperature. The solution was concentrated under reduced pressure and the residue chromatographed (silica gel, 1-3% MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. ¹H NMR (CDCl₃) δ 7.63 (d, 2H, J=8 Hz), 7.52 (s, 1H), 7.06-7.33 (m, 7H), 6.90 (s, 1H), 5.89 (br s, 1H), 5.21 (s, 2H), 3.55-3.76 (m, 6H), 3.43-3.53 (m, 2H), 3.28-3.40 (m, 2H), 3.09 (d, 1H, J=11 Hz), 2.91 (d, 1H, J=11 Hz), 2.71-2.86 (m, 3H), 2.53-2.70 (m, 4H), 2.36-2.46 (m, 1H), 2.25 (t, 1H, J=11 Hz), 2.15 (t, 1H, J=11 Hz), 2.71-2.93 (m, 2H). FAB MS 555 (M+1)
- 20

- 25 Anal. calcd for C₃₂H₃₈N₆O₃•0.30 H₂O•0.30 CHCl₃:

C, 65.10; H, 6.58; N, 14.10;

Found C, 65.16; H, 6.59; N, 13.86.

- Using the methods described in Examples 2 and 4, the following compounds were prepared:
- 30

1-Phenethyl-*cis*-3-[N-(benzyl)carbamoyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

FAB MS 575 (M + 1)

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Anal. calcd for $C_{35}H_{38}N_6O_2 \cdot 0.2 H_2O \cdot 0.35 CH_2Cl_2$:

C, 69.83; H, 6.48; N, 13.82;

Found: C, 69.82; H, 6.46; N, 13.53.

5 1-Phenethyl-*cis*-3-[N-(cyclopropyl)carbamoyl]-5-[N-(1-(4-
cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
 FAB MS 524 (M + 1)

Anal. calcd for $C_{31}H_{36}N_6O_2 \cdot 0.5 H_2O \cdot 0.25 EtOAc$:

C, 69.17; H, 7.07; N, 15.12;

10 Found: C, 69.22; H, 6.86; N, 15.12.

1-Phenethyl-*cis*-3-[N-(*t*-butyl)carbamoyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethyl]carbamoyl] piperidine
FAB MS 541 (M + 1)

15 Anal. calcd for $C_{32}H_{40}N_6O_2 \cdot 0.2 H_2O \cdot 0.25 CH_2Cl_2$:

C, 68.49; H, 7.29; N, 14.86;

Found: C, 68.48; H, 7.27; N, 14.51.

1-(2,2-Diphenylethyl)-*cis*-3-[N-(*t*-butyl)carbamoyl]-5-[N-(
20 cyanobenzyl)-1H-imidazol-5-ylethyl]carbamoyl] piperidine
FAB MS 617 (M + 1)

Anal. calcd for $C_{38}H_{44}N_6O_2 \cdot 1.05 H_2O$: C, 71.80; H, 7.31; N, 13.22;

Found: C, 71.76; H, 7.34; N, 12.83.

25 1-(2,2-Diphenylethyl)-cis-3-[N-(1-morpholinyl)carbamoyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS 631 (M + 1)

Anal. calcd for $C_{38}H_{42}N_6O_3 \cdot 0.4 H_2O \cdot 0.4 EtOAc$:

C, 70.65; H, 6.89; N, 12.48;

30 Found: C, 70.63; H, 6.63; N, 12.46.

Separation of the diastereomers of this compound on a Chiralcel OD HPLC column eluting with hexane/0.1% DEA: ethanol, 55:45 provided the following:

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1-(2,2-Diphenylethyl)-*cis*-3-(R)-[N-(1-morpholinyl)carbamoyl]-5-(S)-
[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

FAB MS 576 (M + 1)

Anal. calcd for C₃₅H₃₇N₅O₃•0.9 H₂O: C, 71.02; H, 6.61; N, 11.83;

5 Found: C, 71.08; H, 6.35; N, 11.71.

1-(2,2-Diphenylethyl)-*cis*-3(S)-[N-(1-morpholinyl)carbamoyl]-5-(R)-
[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

FAB MS 576 (M + 1)

10 Anal. calcd for C₃₅H₃₇N₅O₃•0.9 H₂O: C, 71.02; H, 6.61; N, 11.83;

Found: C, 71.08; H, 6.35; N, 11.71.

15

EXAMPLE 5

Preparation of N-[1-Phenethyl-*cis*-5-(N'-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl) piperidine-3-carbonyl] methionine
methyl ester

20 The lithium salt of 1-phenethyl-*cis*-3-carboxy-5-[N-(1-(4-
cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (90.0 mg,
0.183 mmol), methionine (43.8 mg, 0.219 mmol), HOOBT (35.8 mg,
0.219 mmol), EDC (42.1 mg, 0.219 mmol), and Et₃N (60 uL, 0.430
mL) were dissolved in DMF (2 mL). The above solution was stirred
25 overnight at ambient temperature. The solution was concentrated under
reduced pressure and the residue chromatographed (silica gel, 1-2.5%
MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. ¹H NMR
(CDCl₃) δ 7.63(d, 2H, J=8 Hz), 7.51 (s, 1H), 7.10-7.33 (m, 7H), 6.90
(s, 1H), 6.50-6.63 (m, 1H), 6.11-6.36 (m, 1H), 5.21 (s, 2H), 4.65-4.75
30 (m, 1H), 3.75 (s, 3H), 3.25-3.48 (m, 2H), 2.95-3.11 (m, 2H), 2.73-2.83
(m, 2H), 2.53-2.71 (m, 4H), 2.45-2.52 (m, 3H), 2.35-2.44 (m, 1H),
1.93-2.33 (m, 5H), 2.09 (s, 3H), 1.67-1.85 (m, 1H). FAB MS
631(M+1)

Anal. calculated for C₃₄H₄₂N₆O₄S •0.30 CH₂Cl₂:

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C, 62.46; H, 6.52; N, 12.72;
Found C, 62.45; H, 6.53; N, 12.53.

EXAMPLE 6

5

Preparation of N-[1-Phenethyl-*cis*-5-(N'-(1-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamoyl) piperidine-3-carbonyl] methionine

N-[1-Phenethyl-*cis*-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamoyl] piperidine-3-carbonyl] methionine methyl ester (19 mg, 0.030 mmol) was dissolved in THF (2 mL) and H₂O (1 mL). A 1N solution of LiOH·H₂O (30.1 μL, 0.030 mmol) was added and the solution was stirred overnight at ambient temperature. The solution was purified on a RP HPLC VYDAC column (0.1% TFA in CH₃CN: 0.1% TFA in H₂O, 5:95 to 95:5 gradient) and lyophilized to give the title compound as *cis* diastereomers.

Diastereomer A: ¹H NMR (CD₃OD) δ 8.99 (s, 1H), 7.80 (d, 2H, J=8 Hz), 7.51 (s, 1H), 7.47 (d, 2H, J=8 Hz), 7.20-7.37 (m, 5H), 5.61 (s, 2H), 4.26-4.57 (m, 1H), 3.60-3.75 (m, 2H), 3.44-3.55 (m, 1H), 3.30-3.43 (m, 3H), 2.90-3.15 (m, 6H), 2.75-2.85 (m, 2H), 2.48-2.70 (m, 2H), 2.09-2.28 (m, 2H), 2.09 (s, 3H), 1.90-2.08 (m, 1H), 1.61-1.75 (m, 1H). FAB MS 617 (M+1)

Diastereomer B: ¹H NMR (CD₃OD) δ 9.02 (s, 1H), 7.81 (d, 2H, J=8 Hz), 7.53 (s, 1H), 7.51 (d, 2H, J=8 Hz), 7.22-7.39 (m, 5H), 5.62 (s, 2H), 4.29-4.59 (m, 1H), 3.76 (d, 1H, J=8 Hz), 3.68 (d, 1H, J=10 Hz) 3.33-3.52 (m, 4H), 2.95-3.20 (m, 6H), 2.79-2.87 (m, 2H), 2.50-2.68 (m, 2H), 2.05-2.13 (m, 2H), 2.09 (s, 3H), 1.93-2.08 (m, 1H), 1.70-1.82 (m, 1H). FAB MS = 617 (M+1)

EXAMPLE 7

30

Preparation of 1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetyl amino] piperidine

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Step A: Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-(benzyloxycarbonyl)amino piperidine
1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-piperidine-5-

5 carboxylic acid (1.87 g, 6.51 mmol), benzyl alcohol (1.68 mL, 16.3 mmol), diphenyl phosphorylazide (1.47 mL, 6.83 mmol), and Et₃N (0.95 mL, 6.83 mmol) were dissolved in toluene (50 mL). The solution was heated at 90°C for 4 h. The solution was diluted with EtOAc and was washed with Sat. NaHCO₃ solution, water, and brine. The organics were dried (MgSO₄), filtered, and concentrated to give the title
10 compound without further purification.

Step B: Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-amino piperidine
1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-

15 (benzyloxycarbonyl)amino piperidine (2.55 g, 6.51 mmol) was dissolved in EtOAc (75 mL), treated with Pd/C (510 mg) and shaken on a Parr apparatus at 45 psi overnight. The reaction mixture was filtered through celite, concentrated, and chromatographed (silica gel, 2% MeOH/CH₂Cl₂ with NH₄OH) to give the title compound.

20

Step C: Preparation of 1H-Imidazole-4- acetic acid methyl ester
hydrochloride

A solution of 1H-imidazole-4-acetic acid hydrochloride (4.00g, 24.6 mmol) in methanol (100 ml) was saturated with gaseous
25 hydrogen chloride. The resulting solution was allowed to stand at room temperature (RT) for 18hr. The solvent was evaporated in vacuo to afford the title compound as a white solid.

¹H NMR(CDCl₃, 400 MHz) δ 8.85(1H, s), 7.45(1H, s), 3.89(2H, s) and 3.75(3H, s) ppm.

30

Step D: Preparation of 1-(Triphenylmethyl)-1H-imidazol-4-ylacetic
acid methyl ester

To a solution of 1H-imidazole-4- acetic acid methyl ester hydrochloride (24.85g, 0.141mol) in dimethyl formamide (DMF)

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(115ml) was added triethylamine (57.2 ml, 0.412mol) and triphenylmethyl bromide(55.3g, 0.171mol) and the suspension was stirred for 24hr. After this time, the reaction mixture was diluted with ethyl acetate (EtOAc) (1 l) and water (350 ml). The organic phase was washed with sat. aq. NaHCO₃ (350 ml), dried (Na₂SO₄) and evaporated in vacuo. The residue was purified by flash chromatography (SiO₂, 0-100% ethyl acetate in hexanes; gradient elution) to provide the title compound as a white solid.

¹H NMR (CDCl₃, 400 MHz) δ 7.35(1H, s), 7.31(9H, m), 7.22(6H, m), 6.76(1H, s), 3.68(3H, s) and 3.60(2H, s) ppm.

Step E: Preparation of [1-(4-Cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester

To a solution of 1-(triphenylmethyl)-1H-imidazol-4-ylacetic acid methyl ester (8.00g, 20.9mmol) in acetonitrile (70 ml) was added bromo-p-toluenitrile (4.10g, 20.92 mmol) and heated at 55°C for 3 hr. After this time, the reaction was cooled to room temperature and the resulting imidazolium salt (white precipitate) was collected by filtration. The filtrate was heated at 55°C for 18hr. The reaction mixture was cooled to room temperature and evaporated in vacuo. To the residue was added EtOAc (70 ml) and the resulting white precipitate collected by filtration. The precipitated imidazolium salts were combined, suspended in methanol (100 ml) and heated to reflux for 30min. After this time, the solvent was removed in vacuo, the resulting residue was suspended in EtOAc (75ml) and the solid isolated by filtration and washed (EtOAc). The solid was treated with sat aq NaHCO₃ (300ml) and CH₂Cl₂ (300ml) and stirred at room temperature for 2 hr. The organic layer was separated, dried (MgSO₄) and evaporated in vacuo to afford the title compound as a white solid :

¹H NMR(CDCl₃, 400 MHz) δ 7.65(1H, d, J=8Hz), 7.53(1H, s), 7.15(1H, d, J=8Hz), 7.04(1H, s), 5.24(2H, s), 3.62(3H, s) and 3.45(2H, s) ppm.

Step F: Preparation of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid

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A solution of [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid methyl ester (4.44g, 17.4mmol) in THF (100ml) and 1 M lithium hydroxide (17.4 ml, 17.4 mmol) was stirred at RT for 18 hr. 1 M HCl (17.4 ml) was added and the THF was removed by evaporation in vacuo. The aqueous solution was lyophilized to afford the title compound containing lithium chloride as a white solid. ¹H NMR(CD₃OD, 400 MHz) δ 8.22(1H, s), 7.74(1H, d, J=8.4Hz), 7.36(1H, d, J=8.4Hz), 7.15(1H, s), 5.43(2H, s) and 3.49(2H, s) ppm.

10

Step G: Preparation of 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetylaminol]-piperidine

15 1-(t-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-amino piperidine (134 mg, 0.520 mmol), [1-(4-cyanobenzyl)-1H-imidazol-5-yl]acetic acid (147 mg, 0.520 mmol), HOBT (73.8 mg, 0.546 mmol), EDC (104 mg, 0.546 mmol), and Et₃N (65.2 uL, 0.468 mmol) were dissolved in DMF (4mL) and stirred at ambient temperature overnight. The solution was concentrated under reduced pressure and the residue was chromatographed (silica gel, 0.5-2% MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. ¹H NMR (CDCl₃) δ 7.64 (d, 2H, J=8 Hz), 7.52 (s, 1H), 7.19 (d, 2H, J=8 Hz), 6.90-7.05 (m, 1H), 6.98 (s, 1H), 5.22-5.35 (m, 2H), 3.78-3.91 (m, 2H), 3.69 (s, 3H), 3.57-3.64 (m, 1H), 3.45-3.56 (m, 1H), 3.34 (s, 2H), 3.05-3.30 (m, 1H), 2.55-2.68 (m, 1H), 2.05-2.13 (m, 1H), 1.55-1.70 (m, 1H), 1.42 (s, 9H). FAB MS 482 (M+1).

25

Anal. calculated for C₂₅H₃₁N₅O₅•0.90 H₂O:

C, 60.32; H, 6.64; N, 14.07;

Found C, 60.38; H, 6.36; N, 13.78.

30

EXAMPLE 8

Preparation of 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetylaminol] piperidine

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Step A: Preparation of *cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetylamino] piperidine
1-(*t*-Butoxycarbonyl)-3-methoxycarbonyl-5-[N-(1-(4-

5 cyanobenzyl)-1H-imidazol-5-yl)acetylamino] piperidine (44.6 mg, 0.093 mmol) was dissolved in CH₂Cl₂ (6 mL). Trifluoroacetic acid (3 mL) was added and the solution was stirred at ambient temperature for 4 h. The solution was concentrated under reduced pressure to give the title compound without further purification.

10

Step B: Preparation of 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetylamino] piperidine

15 *cis*-3-Methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)acetylamino] piperidine (35.3 mg, 0.093 mmol), benzaldehyde (32.5 μ L, 0.278 mmol), and sodium cyanoborohydride (17.5 mg, 0.278 mmol) was dissolved in MeOH (2 mL) and stirred overnight at ambient temperature. The solution was concentrated under reduced pressure and chromatographed (silica gel, 0.5-2%
20 MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. ¹H NMR (CDCl₃) δ 7.62 (d, 2H, J=8 Hz), 7.52 (s, 1H), 7.11-7.31 (m, 7H), 6.99 (s, 1H), 6.25 (br s, 1H), 5.24 (s, 2H), 3.86-3.96 (m, 1H), 3.65 (s, 3H), 3.29 (s, 2H), 2.48-2.83 (m, 8H), 2.13-2.24 (m, 1H), 1.83-1.95 (m, 1H), 1.50-1.65 (m, 1H). FAB MS 486 (M+1)

25 Anal. calculated for C₂₈H₃₁N₅O₃•0.30 H₂O•0.25 CHCl₃:

C, 65.15; H, 6.16; N, 13.45;

Found C, 65.18; H, 6.15; N, 13.46.

30 Using the methods described in Examples 7 and 8, but substituting 1-(*t*-butoxycarbonyl)-piperidine-3(S)-carboxylic acid for 1-(*t*-butoxycarbonyl)-*cis*-3-methoxycarbonyl-piperidine-5- carboxylic acid in Ex. 7, Step A, and diphenylacetaldehyde for phenylacetaldehyde in Ex. 8, Step B, the following compound was prepared:

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1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine

Anal. calculated for $C_{32}H_{33}N_5O \cdot 0.30 H_2O$:

C, 75.50; H, 6.65; N, 13.62;

Found C, 75.51; H, 6.79; N, 13.76.

5

FAB MS (M+1) 504

Using the methods described for Examples 7 and 8, but substituting 1H-imidazole-4-propionic acid for 1H-imidazole-4-acetic acid in Ex. 7, Step C, the following compound was prepared:

10

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylpropionyl)amino] piperidine

Anal. calculated for $C_{33}H_{35}N_5O \cdot 0.55 H_2O$:

15

C, 75.13; H, 6.90; N, 13.72;

Found C, 75.15; H, 6.89; N, 13.40.

FAB MS (M+1) 518

Using the methods described for Examples 7 and 8, but substituting 1H-imidazole-4-carboxylic acid for 1H-imidazole-4-acetic acid in Ex. 7, Step C, the following compound was prepared:

20

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylcarbonyl)amino] piperidine

25

FAB MS (M+1) 490

EXAMPLE 9

30 Preparation of 1-(Diphenylacetyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

cis-3-Methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (86.8 mg, 0.219 mmol)
(EXAMPLE 2, Step A) diphenyl acetic acid (302 mg, 1.42 mmol),

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HOBT (54.3 mg, 0.328 mmol), EDC (63 mg, 0.328 mmol), and Et₃N (392 μ L, 5.34 mmol) were dissolved in DMF (4 mL) and stirred at ambient temperature for 5 days. The solution was concentrated, the residue was taken up in EtOAc, washed with sat. NaHCO₃ solution, water, and brine. The organics were dried (MgSO₄), concentrated, and chromatographed (silica gel, 0.5-2% MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. FAB MS = 590 (M+1)
Anal. calculated for C₃₅H₃₅N₅O₄•0.35 CHCl₃•0.20 H₂O:

C, 66.86; H, 5.67; N, 11.03;
Found C, 66.86; H, 5.67; N, 11.01.

Using the methods described above but substituting 3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (Example 11, Step E) as the starting material and the requisite acid, the following compounds were prepared:

1-(Phenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

FAB MS (M+1) 456

1-(Diphenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for C₃₃H₃₃N₅O₂•0.45 CH₂Cl₂•0.10 H₂O:

C, 70.28; H, 6.01; N, 12.25;
Found C, 70.24; H, 5.91; N, 12.09.

1-(3-Chlorobenzoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for C₂₆H₂₆N₅O₂Cl: C, 64.03; H, 5.64; N, 14.36;

Found C, 64.09; H, 5.39; N, 14.12.

FAB MS (M+1) 476

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EXAMPLE 10

Preparation of 1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5

Step A: Preparation of 1-(2,2-Diphenylethyl)-3-carboxy piperidine

Nipecotic acid (300 mg, 2.38 mmol), diphenylacetaldehyde (1.26 mL, 7.13 mmol), sodium cyanoborohydride (448 mg, 7.13 mmol), and HOAc (204 uL, 3.57 mmol) were dissolved in MeOH (20 mL) and stirred at ambient temperature overnight. The solution was concentrated under reduced pressure, take up in ether and 1N NaOH, extract with ether (3X), acidify the aqueous layer with 1N HCl, and extract with EtOAc (3X). The EtOAc layers were dried (MgSO₄) and concentrated to give the title compound without further purification.

15

Step B: Preparation of 1-(2,2-Diphenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-3-carboxy piperidine (472 mg, 1.52 mmol), 3-(4-cyanobenzyl) histamine (456 mg, 1.52 mmol) (EXAMPLE 1, Step E) HOBt (216 mg, 1.60 mmol), EDC (307 mg, 1.60 mmol), and Et₃N (637 uL, 4.57 mmol) were dissolved in DMF (10 mL) and was stirred overnight at ambient temperature. The solution was concentrated under reduced pressure and chromatographed (silica gel, 0.5-2% MeOH/CH₂Cl₂ with NH₄OH) to give the title compound. ¹H NMR (CDCl₃) δ 7.96 (br s, 1H), 7.60 d, 2H, J=8 Hz), 7.46 (s, 1H), 7.09-7.37 (m, 12H), 6.74 (s, 1H), 5.20 (s, 2H), 4.26 (t, 1H, J=8 Hz), 3.05-3.17 (m, 2H), 2.93-3.04 (m, 1H), 2.78-2.91 (m, 2H), 2.49-2.61 (m, 1H), 2.24-2.47 (m, 1H), 2.15-2.30 (m, 2H), 1.95-2.14 (m, 2H), 1.86 (d, 1H, J=12 Hz), 1.29-1.55 (m, 3H). FAB MS 518 (M+1)

Anal. calculated for C₃₃H₃₅N₅O₁•0.35 CHCl₃•0.10 H₂O:

25
30

C, 71.37; H, 6.38; N, 12.48;
Found C, 71.41; H, 6.32; N, 12.36.

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EXAMPLE 11

Preparation of 1-(2-(3-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5

Step A: Preparation of S-(-)-Ethyl nipecotate

Racemic ethyl nipecotate (122.5 g, 0.78 mol) was resolved with D-tartaric acid (117 g, 0.78 mol) in 95% EtOH (611 mL) following the procedure described by P. Magnus et al. (J. Org. Chem. 1991, 56, 1166-1170) to give S-(-)-ethyl nipecotate.

10

Step B: Preparation of Ethyl 1-(t-butoxycarbonyl)piperidine-3(S)-carboxylate

S-(-)-Ethyl nipecotate (20.0 g, 0.127 mol) was dissolved in THF (250 mL)- H₂O (250 mL) at ambient temperature and treated with NaHCO₃ (32.0 g, 0.381 mol) and di-*tert*-butyl-dicarbonate (43.8 mL, 0.190 mol). After stirring for 16 h, the reaction mixture was concentrated to remove THF and extracted with EtOAc (2 x 200 mL). The organics were combined, washed with brine, dried (MgSO₄), filtered and concentrated to give the title compound.

15

20

Step C: Preparation of 1-(tert-Butoxycarbonyl)piperidine-3(S)-carboxylic acid

Ethyl 1-(t-butoxycarbonyl)piperidine-3(S)-carboxylate (35.9 g, 0.099 mol) was dissolved in abs EtOH (70 mL), treated with 0.5N NaOH (418 mL, 0.209 mol), and heated at reflux for 0.75 h. The reaction mixture was cooled and extracted with EtOAc. The aqueous basic layer was cooled with ice, carefully acidified (pH 3) with 3N HCl and extracted with CH₂Cl₂ (3 x 100 mL). The organics were combined, dried (MgSO₄), filtered, and concentrated to give the title compound.

25

30

Step D: Preparation of 1-(tert-Butyloxycarbonyl)-3(S)-[N-1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl]carbamoyl] piperidine

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1-(tert-Butoxycarbonyl)piperidine-3(S)-carboxylic acid (5.06 g, 0.022 mol) and 3-(4-cyanobenzyl)histamine (Example 1, Step E) (6.6 g, 0.022 mol) were dissolved in DMF (30 mL) at ambient temperature and treated with EDC (5.07 g, 0.026 mol), HOBT (3.58 g, 0.26 mol), and N-methylmorpholine (12.12 mL, 0.11 mol). After stirring for 18 hr, the reaction mixture was partitioned between EtOAc (500 mL)-aq satd NaHCO₃ soln, the organic layer separated, washed with satd NaHCO₃ soln, H₂O, brine, dried (MgSO₄), filtered and concentrated to give the title compound which was used without further purification.

10

Step E: Preparation of 3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazole-5-ethyl)carbamoyl] piperidine dihydrochloride

1-(tert-Butyloxycarbonyl)-3(S)-[N-1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl]carbamoyl] piperidine (9.25 g, 0.021 mol) was dissolved in EtOAc (500 mL) with stirring at 0°C. in an ice-water bath. HCl gas was bubbled through the solution for 5 min., the flask stoppered, and the solution stirred for 1 hr. The solution was purged with N₂ then concentrated to dryness to give the title compound. ¹H NMR (CD₃OD); δ 9.02 (s, 1H), 7.80 (d, 2H, J = 8 Hz), 7.52 (s, 1H), 7.48 (d, 2H, J = 8 Hz), 5.62 (s, 2H), 3.42 (td, 2H, J = 3, 7 Hz), 3.00-3.26 (m, 4H), 2.80 (t, 2H, J = 7 Hz), 2.67-2.78 (m, 1H), 1.65 - 2.0 (m, 4H). FAB MS 338 (M+1).

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Step F: Preparation of 2-(3-Chlorophenyl)-2-phenyl oxirane

A 250 mL-round bottom flask was charged with NaH (60% dispersion in mineral oil) (1.92 g, 0.048 mol), washed with petroleum ether, then treated with dry DMSO (40 mL) under N₂. To this reaction mixture was added trimethylsulfoxonium iodide (10.56 g, 0.048 mol) through a solid addition funnel over 15 min. After stirring for 0.5 hr, a solution of 3-chlorobenzophenone (8.66 g, 0.04 mol) in DMSO (15 mL) was added dropwise, and the mixture was heated at 55°C. for 2 hr. The mixture was added to ice-water, extracted with ether (3 x 100 mL), the organics combined, dried (MgSO₄), filtered, and concentrated to give the title compound.

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Step G: Preparation of 2-(3-Chlorophenyl)-2-phenyl
carboxaldehyde

2-(3-Chlorophenyl)-2-phenyl oxirane (10.19 g, 0.04 mol)
5 was dissolved in dry benzene (250 mL), treated with $\text{BF}_3 \cdot \text{etherate}$ (0.2 mL) and stirred at ambient temperature for 1 hr. The benzene was extracted with H_2O until the aqueous layer was no longer acidic, then concentrated to dryness to give the title compound after chromatography (5% EtOAc/hexane on SiO_2). ^1H NMR (CDCl_3) δ 9.95
10 (s, 1H), 7.1 - 7.5 (m, 9H), 4.85 (s, 1H).

Step H: Preparation of 1-(2-(3-Chlorophenyl)-2-phenylethyl)-3-
(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
15 ylethyl)carbamoyl] piperidine dihydrochloride (0.256 g, 0.623 mmol) was dissolved in MeOH (10 mL), the pH adjusted to 5 with Et_3N , and 2-(3-chlorophenyl)-2-phenylcarboxaldehyde (0.427 g, 1.87 mmol) and NaCNBH_3 (0.078 g, 1.25 mmol) were added. After stirring for 18 hr
20 at ambient temperature, the reaction mixture was partitioned between EtOAc and satd NaHCO_3 soln, the organic layer separated, washed with H_2O , brine, dried (MgSO_4), filtered and concentrated to dryness to give the title compound after chromatography on SiO_2 eluting with 3%
25 MeOH/ CH_2Cl_2 w/ NH_4OH . ^1H NMR (CD_3OD); δ 7.88 (br s, 1H), 7.60 (d, 2H, $J = 8$ Hz), 7.47 (s, 1H), 7.07 - 7.36 (m, 11H), 6.76 (d, 1H, $J = 2.7$ Hz), 5.21 (s, 2H), 4.24 (td, 1H, $J = 2, 8$ Hz), 2.80-3.13 (m, 5H), 2.50 - 2.65 (m, 1H), 2.44 (s, 1H), 2.0 - 2.3 (m, 4H), 1.86 (d, 1H, $J = 12$ Hz), 1.3 - 1.55 (m, 3H). FAB MS 552 ($\text{M}+1$).

Anal. calculated for $\text{C}_{33}\text{H}_{34}\text{N}_5\text{OCl} \cdot 0.40 \text{ H}_2\text{O}$:

30 C, 70.87; H, 6.27; N, 12.52;
Found C, 70.84; H, 6.31; N, 12.39.

Using the methods described above, but substituting the requisite ketone in Step F, the following compounds were prepared:

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1-(Dibenzylsuberyl)methyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{35}H_{37}N_5O \cdot 0.45 H_2O$:

5 C, 76.18; H, 6.92; N, 12.69;
Found C, 76.15; H, 6.84; N, 12.49.

1-(2-(3-Methylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 Anal. calculated for $C_{34}H_{37}N_5O \cdot 0.40 H_2O$:

C, 75.78; H, 7.07; N, 13.00;
Found C, 75.81; H, 7.01; N, 13.20

1-(2-(3-Trifluoromethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15

Anal. calculated for $C_{34}H_{34}N_5OF_3 \cdot 0.20 H_2O$:

C, 69.30; H, 5.88; N, 11.88;
Found C, 69.32; H, 5.84; N, 12.04.

1-(2-(2-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20

Anal. calculated for $C_{33}H_{34}N_5OCl \cdot 0.50 H_2O$:

C, 70.64; H, 6.29; N, 12.48;
Found C, 70.67; H, 6.16; N, 12.50.

1-(2-(4-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25

Anal. calculated for $C_{33}H_{34}N_5OCl$: C, 70.98; H, 6.26; N, 12.54;

Found C, 71.02; H, 6.22; N, 12.40.

1-(2-(3-Aminomethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30

Anal. calculated for $C_{34}H_{38}N_6O \cdot 4.25 CF_3CO_2H \cdot 0.45 H_2O$:

C, 49.11; H, 4.18; N, 8.09;

- 117 -

Found C, 49.11; H, 4.16; N, 8.15.

Using the methods described above, but substituting commercially available aldehydes for 2-(3-chlorophenyl)-2-phenylcarboxaldehyde in
5 Step H, the following compounds were prepared:

1-(2-Phenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

FAB MS (M+1) 442

10

1-(2-Phenethyl)-3(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{27}H_{31}N_5O \cdot 2.0 HCl \cdot 1.60 H_2O$:

C, 59.69; H, 6.72; N, 12.89;

15

Found C, 59.72; H, 7.18; N, 11.91.

FAB MS (M+1) 442

1-(3-Phenylpropyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

20 Anal. calculated for $C_{28}H_{33}N_5O \cdot 2.75 CF_3CO_2H \cdot 0.75 H_2O$:

C, 51.14; H, 4.80; N, 8.95;

Found C, 51.42; H, 4.78; N, 9.00.

FAB MS (M+1) 456

25 1-(2-Benzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{26}H_{29}N_5O \cdot 2.80 CF_3CO_2H \cdot 0.70 H_2O$:

C, 49.98; H, 4.41; N, 9.22;

Found C, 49.98; H, 4.39; N, 9.67.

30 FAB MS (M+1) 428

1-(2-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{26}H_{28}N_5OCl \cdot 3.25 CF_3CO_2H \cdot 0.50 H_2O$:

- 118 -

C, 46.38; H, 3.86; N, 8.32;
Found C, 46.39; H, 3.82; N, 8.54.

FAB MS (M+1) 462

- 5 1-(3-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{26}H_{28}N_5OCl \cdot 2.75 CF_3CO_2H \cdot 0.40 H_2O$:

C, 48.33; H, 4.06; N, 8.95;

Found C, 48.30; H, 4.06; N, 9.16.

- 10 FAB MS (M+1) 462

1-(3-Chlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{26}H_{28}N_5OCl \cdot 0.45 H_2O$:

- 15 C, 66.43; H, 6.20; N, 14.90;

Found C, 66.43; H, 6.07; N, 14.97.

1-(2,2-Diphenyl-2-hydroxyethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

- 20 Anal. calculated for $C_{33}H_{35}N_5O_2 \cdot 0.25 H_2O$:

C, 73.65; H, 6.65; N, 13.01;

Found C, 73.69; H, 6.79; N, 12.84.

FAB MS (M+1) 534

- 25 1-(3-Methoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

FAB MS (M+1) 458

- 30 1-(3,5-Dichlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{26}H_{27}N_5OCl_2 \cdot 0.40 H_2O$:

C, 62.01; H, 5.56; N, 13.91;

Found C, 61.98; H, 5.55; N, 13.57.

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1-(3-Trifluoromethoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{27}H_{28}N_5O_2F_3 \cdot 2.0 \text{ HCl} \cdot 1.85 \text{ H}_2\text{O}$:

C, 52.49; H, 5.50; N, 11.34;

5

Found C, 52.50; H, 5.72; N, 11.34.

1-(2,5-Dimethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{28}H_{33}N_5O \cdot 0.40 \text{ H}_2\text{O}$:

10

C, 72.67; H, 7.36; N, 15.13;

Found C, 72.67; H, 7.27; N, 14.77.

1-(3-Trifluoromethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 Anal. calculated for $C_{27}H_{28}N_5OF_3 \cdot 0.15 \text{ H}_2\text{O}$:

C, 65.09; H, 5.73; N, 14.06;

Found C, 65.14; H, 5.83; N, 14.01.

1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20

Anal. calculated for $C_{26}H_{28}N_5OBr \cdot 2.0 \text{ HCl} \cdot 1.0 \text{ H}_2\text{O}$:

C, 52.28; H, 5.40; N, 11.72;

Found C, 52.33; H, 5.51; N, 11.26.

1-(3-Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1-H-imidazol-5-ylethyl)carbamoyl] piperidine

25

Anal. calculated for $C_{27}H_{31}N_5O \cdot 2.0 \text{ HCl} \cdot 1.30 \text{ H}_2\text{O}$:

C, 60.54; H, 6.70; N, 13.07;

Found C, 60.58; H, 6.68; N, 12.22.

30

1-Isobutyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{23}H_{31}N_5O \cdot 2.3 \text{ HCl} \cdot 0.95 \text{ H}_2\text{O}$:

C, 55.87; H, 7.17; N, 14.16;

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Found C, 55.91; H, 7.38; N, 14.01.

FAB MS (M+1) 394

5 1-(2-Methyl-2-phenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{34}H_{37}N_5O \cdot 0.40 H_2O$:

C, 75.78; H, 7.07; N, 13.00;

Found C, 75.81; H, 7.01; N, 13.20.

FAB MS (M+1) 532

10

Using the methods described above, but substituting 1-morpholinyl- α -phenylacetaldehyde or 1-piperidinyl- α -phenylacetaldehyde (prepared following the procedure described by L. Duhamel, P. Duhamel, P. Siret, Bull. Soc. Chim. Fr., [7-8], 2460-2466 (1973)) in Step H, the following compounds were prepared:

15

1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine-Diastereomer A

Anal. calculated for $C_{31}H_{38}N_6O_2 \cdot 0.80 H_2O \cdot 0.25 EtOAc$:

20

C, 68.25; H, 7.45; N, 14.92;

Found C, 68.27; H, 7.13; N, 14.92.

1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine-Diastereomer B

25

Anal. calculated for $C_{31}H_{38}N_6O_2 \cdot 0.65 H_2O$:

C, 69.16; H, 7.36; N, 15.61;

Found C, 69.15; H, 7.31; N, 15.48.

30 1-(2-(1-Piperidinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

FAB MS (M+1) 525

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Using the methods described in Examples 11 and 1, but substituting 2-methylhistamine for the starting material in Ex.1, Step E, the following compound was prepared:

- 5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{34}H_{37}N_5O \cdot 0.45 H_2O$:

C, 75.65; H, 7.08; N, 12.97;

Found C, 75.65; H, 6.93; N, 12.68.

10

Using the methods described in Examples 11 and 1, but substituting 4-methoxybenzyl bromide for 4-cyanobenzyl bromide in Ex.1, Step E, the following compound was prepared:

- 15 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-methoxybenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{33}H_{38}N_4O_2 \cdot 2.0 HCl \cdot 1.40 H_2O$:

C, 63.84; H, 6.95; N, 9.02;

Found C, 63.91; H, 7.33; N, 9.45.

20

EXAMPLE 12

Preparation of 1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25

- 3(S)-[N-1-(4-Cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine dihydrochloride (Example 11, Step E) (0.203 g, 0.494 mmol) was dissolved in DMF (10 mL), treated with K_2CO_3 (0.503 g, 1.976 mmol) and bromodiphenylmethane (0.134 g, 0.543 mmol), and stirred for 48 hr at ambient temperature. The reaction mixture was concentrated, dissolved in EtOAc, washed with aq satd $NaHCO_3$ soln, H_2O , brine, and dried ($MgSO_4$), filtered and concentrated to give the title compound after SiO_2 chromatography
- 30

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eluting with 0-3% MeOH: CH₂Cl₂ with NH₄OH. Anal. calculated for C₃₂H₃₃N₅O • 0.75 H₂O:

C, 74.31; H, 6.72; N, 13.54;
Found C, 74.37; H, 6.48; N, 13.37.

5 FAB MS (M+1) 504.

Using the method described above, but substituting the requisite bromide or mesylate for bromodiphenylmethane, the following compounds were prepared:

10

1-(3-Methoxyphenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for C₂₈H₃₃N₅O₂ • 2 HCl • 1.95 H₂O:

C, 58.02; H, 6.76; N, 12.08;
15 Found C, 58.01; H, 7.03; N, 11.99.

FAB MS (M+1) 472.

1-(1-Naphthylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

20 Anal. calculated for C₃₁H₃₃N₅O • 0.90 H₂O:

C, 73.32; H, 6.91; N, 13.79;
Found C, 73.32; H, 7.04; N, 13.46.

1-(3-Chlorophenethyl)-3(S)-[N-1-(4- cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

25 Anal. calculated for C₂₇H₃₀N₅OCl • 2 HCl • 1.65 H₂O:

C, 56.04; H, 6.15; N, 12.10;
Found C, 56.09; H, 6.43; N, 11.77.

30 1-(α -Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
ylethyl)carbamoyl] piperidine

Anal. calculated for C₂₇H₃₁N₅O • 0.45 H₂O:

C, 72.12; H, 7.15; N, 15.57;
Found C, 71.80; H, 6.81; N, 15.96.

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FAB MS (M+1) 442.

Using the methods described in Examples 12 and 1, but substituting 2-methylhistamine for the starting material in Ex.1, Step E, the following
5 compound was prepared:

1-(2-Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{33}H_{35}N_5O \cdot 0.40 \text{ EtOAc}$:

10 C, 75.11; H, 6.96; N, 12.66;

Found C, 75.15; H, 7.24; N, 12.60.

FAB MS (M+1) 518.

EXAMPLE 13

15

Preparation of 1-(α -Toluenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-
imidazol-5-ylethyl)carbamoyl] piperidine

3(S)-[N-1-(4-Cyanobenzyl)-1H-imidazol-5-
20 ylethyl)carbamoyl] piperidine dihydrochloride (Example 11, Step E)
(0.210 g, 0.512 mmol) was dissolved in CH_2Cl_2 (6 mL), treated with
 Et_3N (0.285 mL, 2.046 mmol) and α -toluenesulfonyl chloride (0.195 g,
1.023 mmol) and stirred at ambient temperature for 2 hr. The reaction
mixture was concentrated to dryness, partitioned between EtOAc and
25 satd NaHCO_3 soln, the organic layer separated, washed with brine, and
dried (MgSO_4). Filtration and concentration to dryness gave the title
compound after purification on a Waters Prep Pak eluting with
0.1%TFA/ H_2O : 0.1%TFA/ CH_3CN , 95:5 to 5:95. ^1H NMR (CD_3OD); δ
8.80 (s, 1H), 8.02 - 8.12 (m, 1H), 7.78 (d, 2H, $J=8$ Hz), 7.34 - 7.5 (m,
30 7H), 5.54 (s, 2H), 4.32 (s, 2H), 3.2-3.56 (m, 4H), 2.65 - 2.95 (m, 4H),
2.25-2.4 (m, 1H), 1.4 - 1.8 (m, 4H). FAB MS 492 (M+1).

Using this procedure, but substituting the sulfonyl chloride, the
following compounds were prepared:

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1-(Benzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS (M+1) 478.

5

1-(1-Naphthylenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
Anal. calculated for $C_{29}H_{29}N_5O_3S \cdot 1.50 CF_3CO_2H \cdot 0.10 H_2O$:

C, 54.87; H, 4.42; N, 10.00;

10

Found C, 54.84; H, 4.31; N, 10.19.

1-(3-Chlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
Anal. calculated for $C_{25}H_{26}N_5O_3SCl \cdot 0.55 H_2O$:

15

C, 57.53; H, 5.23; N, 13.42;

Found C, 57.51; H, 5.20; N, 13.28.

1-(3,5-Dichlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20

Anal. calculated for $C_{25}H_{25}N_5O_3SCl \cdot 0.30 H_2O$:

C, 54.41; H, 4.68; N, 12.69;

Found C, 54.43; H, 4.82; N, 12.49.

1-(α -Toluenesulfonyl)-3-(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25

Anal. calculated for $C_{26}H_{29}N_5O_3S \cdot 0.35 H_2O$:

C, 62.72; H, 6.01; N, 14.07;

Found C, 62.73; H, 5.85; N, 13.84.

30

1-(α -Toluenesulfonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
FAB MS (M+1) 550

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1-(Methanesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Anal. calculated for $C_{20}H_{25}N_5O_3S \cdot 0.25 CH_2Cl_2$:

C, 55.68; H, 5.89; N, 16.04;

5 Found C, 56.04; H, 5.89; N, 15.70.

FAB MS (M+1) 416

EXAMPLE 14

10 Preparation of 1-(Diphenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine dihydrochloride (Example 11, Step E)
15 (0.346 g, 0.843mmol) was dissolved in CH_2Cl_2 (10 mL), treated with Et_3N (0.587 mL, 4.2 mmol) and diphenylcarbamoyl chloride (0.390 g, 1.686 mmol) and stirred at ambient temperature for 1 hr. The reaction mixture was concentrated to dryness, partitioned between EtOAc and satd $NaHCO_3$ soln, the organic layer separated, washed with brine, and
20 dried ($MgSO_4$). Filtration and concentration to dryness gave the title compound after purification on a silica gel column eluting with 0 -2% MeOH/ CH_2Cl_2 . Anal. calculated for $C_{32}H_{32}N_6O_2 \cdot 0.95 H_2O$:

C, 69.91; H, 6.22; N, 15.29;

Found C, 69.97; H, 6.15; N, 14.80.

25 FAB MS (M+1) 533.

Using phenylisocyanate in place of diphenylcarbamoyl chloride provided:

1-(Phenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 Anal. calculated for $C_{26}H_{28}N_6O_2 \cdot 0.45 H_2O \cdot 0.45 EtOAc$:

C, 66.21; H, 6.50; N, 16.66;

Found C, 66.18; H, 6.56; N, 16.71.

FAB MS (M+1) 457.

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EXAMPLE 15

Preparation of 1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl]-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Step A: Preparation of Ethyl 1-[2-(2-pyridyl)-2-phenyl-2-hydroxyethyl] piperidine-3(S)- carboxylate
2-(2-pyridyl)-2-phenyl oxirane (prepared following the procedure of Example 11, Step F) (0.106 g, 0.537 mmol) and S-(-)-ethyl nipecotate (0.093 g, 0.591 mmol) in EtOH (0.90 mL) were heated at 50°C. in a sealed tube with stirring for 24 hr. The reaction mixture was dissolved in EtOAc, washed with brine, dried (Na₂SO₄), filtered, and concentrated to dryness to give the title compound.

Step B: Preparation of 1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl] piperidine-3(S)- carboxylic acid
Ethyl 1-[2-(2-pyridyl)-2-phenyl-2-hydroxyethyl] piperidine-3(S)- carboxylate (0.187 g, 0.527 mmol) was dissolved in EtOH (5 mL), 1N NaOH (0.791 mL, 0.791 mmol) and H₂O (5 mL) added, and the reaction mixture heated at reflux for 3 hr. Neutralization with 1N HCl (to a pH of 6) and concentration to dryness gave the title compound which was used without further purification.

Step C: Preparation of 1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl]-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl] piperidine-3(S)-carboxylic acid (0.172 g, 0.527 mmol) was suspended in DMF (5 mL) and treated with EDC (0.106 g, 0.553 mmol), HOBT (0.068 g, 0.501 mmol), followed by N-methylmorpholine to adjust the pH to 7, and 4-(4-Cyanobenzyl) histamine dihydrochloride (0.158 g, 0.527 mmol). stirring at ambient temperature for 18 hr under N₂, the reaction mixture was concentrated, partitioned between CH₂Cl₂ and H₂O, the

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organic phase washed with aq satd NaHCO_3 soln, brine, and dried (Na_2SO_4). Filtration and concentration to dryness gave the title compound after purification by RP HPLC on a Waters Prep Pak eluting with 0.1%TFA/ H_2O : 0.1%TFA/ CH_3CN , 95:5 to 5:95. FAB MS ($\text{M}+1$)

5 535.

Anal. calculated for $\text{C}_{32}\text{H}_{34}\text{N}_6\text{O}_2 \cdot 3.0 \text{ HCl} \cdot 2.10 \text{ H}_2\text{O}$:

C, 56.37; H, 6.09; N, 12.33;

Found C, 56.36; H, 6.14; N, 11.54.

10

EXAMPLE 16

Preparation of 1-(2-Pyridylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoylethyl] piperidine

15 Step A: Preparation of Ethyl 1-(2-pyridylethyl) piperidine-3(S)-carboxylate

S-(-)-Ethyl nipecotate (0.650 g, 4.14 mmol) and 2-vinylpyridine (0.670 mL, 6.21 mmol) were dissolved in n-butanol (50 mL) with stirring under Ar and heated at reflux for 18 hr. The reaction mixture was concentrated, and the residue chromatographed on SiO_2 eluting with CH_2Cl_2 :MeOH, 95:5 to 9:1 to give the title compound. ^1H NMR (CDCl_3); δ 8.52 (dd, 1H, J = 1, 4 Hz), 7.58 (td, 1H, J = 1.8, 8 Hz), 7.26 (s, 1H), 7.18 (d, 1H, J = 8 Hz), 7.106 (dd, 1H, J = 4, 6 Hz), 4.12 (q, 2H, J = 7 Hz), 3.07 (d, 1H, J = 10 Hz), 2.95 - 3.03 (m, 2H), 2.737-2.88 (m, 3H), 2.52 - 2.62 (m, 1H), 2.28 (t, 1H, J = 10 Hz), 2.11 (td, 1H, J = 3, 10 Hz), 1.9 - 2.0 (m, 1H), 1.4 - 1.8 (m, 4H), 1.25 (t, 3H, J = 7 Hz).

30 Step B: Preparation of 1-(2-Pyridylethyl) piperidine-3(S)-carboxylic acid

Following the procedure of Example 15, Step B, the title compound was prepared.

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Step C: Preparation of 1-(2-Pyridylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
Following the procedure of Example 15, Step C, the title compound was prepared. FAB MS (M+1) 413.

5

EXAMPLE 17

Preparation of 1-Phenyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10

Step A: Preparation of Ethyl 1-phenyl-(S)-piperidine carboxylate

To a solution of S-ethyl nipecotate (0.3 g, 1.91 mmol) in CH₂Cl₂ (20 mL) was added triphenylbismuth (1.68 g, 3.82 mmol), copper acetate (0.52 g, 2.86 mmol), and Et₃N (0.39 mL, 2.86 mmol).

15 The resulting mixture was stirred at 25 °C for 18 hr. The reaction was partitioned with CH₂Cl₂ (50ml) and satd NaHCO₃ (30 mL), the organic layer was washed with brine (30ml) and dried (MgSO₄). Filtration and concentration in *vacuo* gave the title compound after SiO₂ chromatography eluting with hexane:ethyl acetate 95:5.

20

Step B: Preparation of 1-Phenyl-(S)-piperidine carboxylic acid

Following the procedure of Example 15, Step B, the title compound was prepared.

25 Step C: Preparation of 1-Phenyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

Following the procedure of Example 15, Step C, the title compound was prepared. Purification was carried out on RP HPLC Waters Prep Pak eluting with 0.1%TFA/H₂O: 0.1%TFA/CH₃CN, 95:5 to 5:95.

30

Anal. calculated for C₂₅H₂₇N₅O • 3.1 CF₃CO₂H • 0.8 H₂O :

C, 47.96; H, 4.09; N, 8.96;

Found C, 47.94; H, 4.12; N, 8.97.

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Using the methods above, but substituting tri-3-methylphenylbismuth for triphenylbismuth, the following compound was prepared:

1-(3-Methylphenyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
5 ylethyl)carbamoylethyl] piperidine

Anal. calculated for $C_{26}H_{29}N_5O \cdot 2.9 CF_3CO_2H \cdot 0.8 H_2O$:

C, 49.44; H, 4.37; N, 9.06;

Found C, 49.43; H, 4.35; N, 9.15.

10

EXAMPLE 18

Preparation of 1-(2,2-Diphenylethyl)-3(S)-[2-(1-(4-cyanobenzyl)-1H-
imidazol-5yl)ethylthiomethyl] piperidine

15 Step A: Preparation of Ethyl 1-(2,2-Diphenylethyl)-3(S)-
piperidine carboxylate

Following the procedure outlined in Example 10, Step A, but using ethyl 3(S)-piperidine carboxylate instead of nipecotic acid, the title compound was prepared.

20

Step B: Preparation of 1-(2,2-Diphenylethyl)-3(S)-hydroxymethyl-
piperidine

25 Ethyl 1-(2,2-Diphenylethyl)-3(S)-piperidine carboxylate (4.90 g, 0.014 mol) dissolved in dry ether (40mL) was added to a suspension of lithium aluminum hydride (1.93 g, 0.051 mol) in dry ether (40mL). The solution was refluxed until the starting material was consumed and then was quenched with saturated potassium sodium tartrate solution (100mL) and stirred for 2 hr. The layers were separated and the aqueous layer extracted with ether (2X). The
30 combined organic extracts were dried ($MgSO_4$) and concentrated to yield the title compound without further purification.

Step C: Preparation of 1-(2,2-Diphenylethyl)-3(S)-tosyloxymethyl-
piperidine

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1-(2,2-Diphenylethyl)-3(S)-hydroxymethyl-piperidine (1.01 g, 3.41 mmol) was dissolved in dry pyridine (25 mL) and tosyl chloride (0.684 g, 3.58 mmol) was added to the solution. After stirring at ambient temperature for 18 hr, the solution was concentrated, the residue taken up in EtOAc, washed with sat. NaHCO₃ solution, H₂O, brine, and dried (MgSO₄). Filtration and concentration gave the title compound without further purification.

Step D: Preparation of 1-(2,2-Diphenylethyl)-3(S)-
10 acetylthiomethyl-piperidine

1-(2,2-Diphenylethyl)-3(S)-tosyloxymethyl-piperidine (1.35 g, 3.23 mmol), potassium thiol acetate (1.47g, 12.9 mmol) and DMF (30mL) were heated at 100°C for 4 hr. The solution was poured into ice and the resulting green precipitate was dissolved in ETOAc.
15 The organics were washed with H₂O (2X), sat. NaHCO₃ solution, brine, dried (MgSO₄) and concentrated to give the title compound without further purification.

Step D: Preparation of the disulfide of 1-(2,2-Diphenylethyl)-3(S)-
20 mercaptomethyl-piperidine

1-(2,2-Diphenylethyl)-3(S)-acetylthiomethyl-piperidine (0.523 g, 1.47 mmol), EtOH (20 mL), and NaOH (0.5N, 20mL) was refluxed 3 hr. The solution was concentrated to remove ethanol and the remaining aqueous solution was decanted from the green oil. The oil
25 was washed with water (2X) and decanted. The oil was dried under reduced pressure to give the title compound without further purification.

Step E: Preparation of 1-(2,2-Diphenylethyl)-3(S)-
30 mercaptomethyl-piperidine

The disulfide (0.10 g, 0.161 mmol) was dissolved in acetone (15mL) and 10% aq. MeOH (10mL). Tributyl phosphine (0.261 mL, 0.322 mmol) was . The solution was stirred for 2 hr, concentrated, and the residue was taken up in EtOAc, washed with satd

NaHCO_3 and dried (MgSO_4). Filtration and concentration gave the title compound without further purification.

Step F: Preparation of 1-Triphenylmethyl-4-(hydroxymethyl)-imidazole

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35.0 g, 260 mmol) in dry DMF (250 ml) at ambient temperature was added Et₃N (90.6 mL, 650 mmol). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g, 273 mmol) in of DMF (500 mL) was added dropwise. The reaction mixture was stirred for 20 hrs, poured over ice, filtered, and washed with ice water. The resulting product was slurried with cold dioxane, filtered, and dried *in vacuo* to provide the title compound as a white solid which was sufficiently pure for use in the next step.

Step G: Preparation of 1-Triphenylmethyl-4-(acetoxymethyl)-imidazole

1-Triphenylmethyl-4-(hydroxymethyl)-imidazole (260 mmol) was suspended in pyridine (500 mL). Acetic anhydride (74 mL, 780 mmol) was added dropwise, and the reaction was stirred for 48 hr during which it became homogeneous. The solution was poured into EtOAc, washed sequentially with water, 5% aqueous HCl solution, satd aqueous NaHCO₃ solution, and brine. The organic extracts were dried (Na₂SO₄), and concentrated *in vacuo* to provide the product as a white powder, which was sufficiently pure for use in the next reaction.

Step H: Preparation of 1-(4-Cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide

1-Triphenylmethyl-4-(acetoxymethyl)-imidazole (85.8 g, 225 mmol) and 4-cyanobenzyl bromide (50.1 g, 232 mmol) in EtOAc (500mL) were stirred at 60 °C for 20 hr, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume (200 mL), reheated at 60 °C for 2

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hrs, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume (100 mL), reheated at 60 °C for another 2hrs, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined,
5 dissolved in methanol (500mL), and warmed to 60 °C. After 2hrs, the solution was concentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid which was used in the next step without further purification.

10

Step I: Preparation of 1-(4-Cyanobenzyl)-5-(hydroxymethyl)-imidazole

1-(4-Cyanobenzyl)-5-(acetoxymethyl)-imidazole hydrobromide (50.4 g, 150 mmol) in 3:1 THF/water (1.5 L) at 0 °C was
15 added lithium hydroxide monohydrate (18.9 g, 450 mmol). After 1hr, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. NaHCO₃ and brine. The solution was then dried (Na₂SO₄), filtered, and concentrated *in vacuo* to provide the crude product as a pale yellow fluffy solid which was sufficiently pure
20 for use in the next step without further purification.

Step J: Preparation of 1-(4-Cyanobenzyl)-5-(chloromethyl)-imidazole

A solution of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-
25 imidazole (1.0g, 4.70mmol), in thionyl chloride (5ml), was stirred at 70°C for 16hrs. The solvent was evaporated in vacuo and the resulting solid suspended in CH₂Cl₂, collected by filtration and dried in vacuo. The material was sufficiently pure to be used without further purification.

30 ¹H NMR CD₃OD δ 9.06 (1H, s), 7.83(2H, d, J=8.0Hz), 7.77(1H, s), 7.55(2H, d, J=8.0Hz), 5.67(2H, s) and 4.78(2H, s) ppm.

Step K: Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethylthiomethyl)] piperidine

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1-(2,2-Diphenylethyl)-3(S)-mercaptomethyl-piperidine (0.322 mmol), 1-(4-cyanobenzyl)-5-(chloromethyl)-imidazole (0.117 g, 0.386 mmol), and diisopropylethylamine (0.168 mL, 0.966 mmol) were dissolved in CH_2Cl_2 (10mL) and refluxed overnight. The solution was concentrated and the residue was taken up in EtOAc, washed with sat. NaHCO_3 , water and brine. The organics were dried (MgSO_4), concentrated, chromatographed (0-3% MeOH, CH_2Cl_2 , NH_4OH), Prep HPLC (100:0 - 5:95 H_2O : CH_3CN w/ 0.1% TFA), free based, and acidified with 1N HCl solution in ether to yield the title compound. ^1H NMR (CD_3OD); δ 9.03 (s, 1H), 7.80 (D, 2H, $J=8\text{Hz}$), 7.65 (s, 1H), 7.50-7.33 (m, 10H), 7.26 (D, 2H, $J=8\text{Hz}$), 5.64 (s, 2H), 4.68 (t, 1H, $J=7\text{Hz}$), 3.98-3.88 (m, 2H), 3.72 (s, 2H), 3.59-3.56 (m, 1H), 3.51-3.47 (m, 1H), 2.87-2.83 (m, 1H), 2.64 (t, 1H, $J=12\text{Hz}$), 2.49-2.42 (m, 1H), 2.35-2.27 (m, 1H), 2.02 (br s, 1H), 1.90-1.77 (m, 3H), 1.19-1.12 (m, 1H). FAB MS 507 (M+1)

Anal. calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{S} \cdot 2.5 \text{HCl} \cdot 1.65 \text{H}_2\text{O}$:
 C, 61.24; H, 6.69; N, 8.93;
 Found C, 61.20; H, 5.93; N, 8.72.

20

EXAMPLE 19

Preparation of 1-(2,2-Diphenylethyl)-3(S)-[2-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethylsulfonylmethyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethylthiomethyl] piperidine (0.050 g, 0.087mmol) was dissolved in MeOH (1mL) and H_2O (1mL), treated with Oxone (0.106 g, 0.173 mmol), and stirred at ambient temperature for 1hr. The solution was concentrated and the residue was taken up in EtOAc, washed with water and brine. The organics were dried (MgSO_4) and chromatographed (RP HPLC Waters Prep Pak, 100:0 - 5:95 H_2O : CH_3CN w/ 0.1% TFA) to give the title compound as a TFA salt. FAB MS 539 (M+1)

Anal. calculated for $\text{C}_{32}\text{H}_{34}\text{N}_4\text{O}_2\text{S} \cdot 3.70 \text{CF}_3\text{CO}_2\text{H} \cdot 0.90 \text{H}_2\text{O}$:
 C, 48.44; H, 4.08; N, 5.74;

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Found C, 48.43; H, 4.06; N, 5.96.

EXAMPLE 20

5 Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-methyl-carbamoyl] piperidine

10 Step A: Preparation of 1-(tert-Butyloxycarbonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-methylcarbamoyl] piperidine

15 1-(tert-Butyloxycarbonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine (Example 11, Step D)(0.100 g, 0.228 mmol) was dissolved in dry DMF (5mL) and cooled in a ice bath. NaH (0.011 g, 0.274 mmol) and CH₃I (0.023 mL, 0.365mmol) were added, and the mixture was stirred at 0°C. for 1.5 hr. The reaction was quenched with water, extracted with EtOAc, the organics washed with H₂O (3X), dried (MgSO₄), and concentrated to give the title compound.

20 Step B: Preparation of 1-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazole-5-ethyl)-N-methylcarbamoyl] piperidine

The title compound was prepared following the procedure outlined in Example 11, Step E.

25 Step C: Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-methylcarbamoyl] piperidine

The title compound was prepared following the procedure outlined in Example 11, Step H. FAB MS (M+1) 532.

30 Anal. calculated for C₃₄H₃₇N₅O • 2.70 CF₃CO₂H • 1.60 H₂O :

C, 54.50; H, 4.98; N, 8.06;

Found C, 54.49; H, 4.97; N, 7.99.

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Using the methods described above the following compound was prepared:

- 1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-
5 N-methyl-carbamoyl] piperidine
FAB MS (M + 1) 520

EXAMPLE 21

- 10 Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)aminomethyl] piperidine

Step A: Preparation of 1-(2,2-Diphenylethyl)-3(S)-piperidine
carboxaldehyde

- 15 1-(2,2-Diphenylethyl)-3(S)-hydroxymethyl-piperidine (Example 18, Step B) (2.10 g, 7.10mmol) and Et₃N (2.97 mL, 21.3 mmol) were dissolved in dry DMSO (40mL) and cooled in an ice bath. Pyridine SO₃ complex (3.39 g, 21.3 mmol) was added slowly, and the solution was stirred for 1hr while allowing to warm to room
20 temperature. The solution was poured into ice water, extracted with CH₂CL₂ (2X), the combined organics washed with satd NaHCO₃ solution, H₂O, brine, and dried (MgSO₄). Filtration and concentration gave the title compound without further purification.

- 25 Step B: Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(cyanobenzyl)-1H-imidazol-5-ylethyl)aminomethyl]-
piperidine

- 1-(2,2-Diphenylethyl)-3(S)-piperidine
carboxaldehyde (0.575 g, 1.96 mmol), 3-(4-cyanobenzyl) histamine
30 dihydrochloride (0.388 g, 1.30 mmol), and NaCNBH₃ (0.123 g, 1.96mmol) were dissolved in MeOH (15mL) and stirred at ambient temperature overnight. The solution was concentrated and the residue taken up in EtOAc, washed with sat. NaHCO₃ solution, H₂O, and brine. The organics were dried, concentrated, and chromatographed (0-4%

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MeOH/CH₂Cl₂/NH₄OH) to give the title compound which was isolated as a tris HCl salt. ¹H NMR (CD₃OD); δ 9.05 (s, 1H), 7.81 (d, 2H, J=8Hz), 7.68 (s, 1H), 7.54 (d, 2H, J=8Hz), 7.49-7.25 (m, 10H), 5.67 (s, 2H), 4.76-7.74 (m, 1H), 4.05-3.88 (m, 3H), 3.54-3.47 (m, 1H), 3.33-3.30 (m, 1H), 3.19-3.15 (m, 2H), 3.02-3.00 (m, 2H), 2.92-2.90 (m, 2H), 2.42 (br s, 1H), 1.99-1.91 (m, 2H), 1.82-1.78 (m, 1H), 1.31-1.28 (m, 2H). FAB MS 504 (M+1).

Anal. calculated for C₃₃H₃₇N₅ • 3.0 HCl • 0.90 H₂O :

C, 62.99; H, 6.70; N, 11.13;

Found C, 63.04; H, 6.83; N, 11.05.

EXAMPLE 22

Preparation of 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

1-Diphenylethyl-3(S)-[N-1(4-cyanobenzyl)-1H-imidazol-5-ylethylaminomethyl]piperidine (0.151 g, 0.246 mmol) and Et₃N (0.154 mL, 1.10 mmol) were dissolved in dry CH₂Cl₂ (15mL) and cooled in an ice bath. A solution of acetyl chloride (0.026 mL, 0.369 mmol) in CH₂Cl₂ (1mL) was added and the reaction was stirred for 18 hr while allowing to warm to room temperature. The solution was diluted with EtOAc, washed with sat. NaHCO₃ solution, H₂O, and brine. The organics were dried (MgSO₄) and concentrated to yield the title compound. ¹H NMR (CDCl₃); δ 7.59 (d, 2H, J=8Hz), 7.52 (s, 1H), 7.49-7.04 (m, 12H), 6.87 (s, 1H), 5.29 (s, 2H), 4.17 (t, 1H, J=7Hz), 3.32-3.25 (m, 1H), 3.21-3.13 (m, 1H), 3.04-2.96 (m, 4H), 2.68-2.49 (m, 4H), 2.24-2.20 (m, 1H), 1.91-1.73 (m, 6H), 1.56-1.50 (m, 1H), 1.46-1.43 (m, 1H), 0.96-0.92 (m, 1H). FAB MS 546 (M+1).

Anal. calculated for C₃₅H₃₉N₅O • 0.70 H₂O :

C, 75.29; H, 7.29; N, 12.54;

Found C, 75.25; H, 7.26; N, 12.06.

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Using the methods described in Examples 21 and 22, but substituting the requisite amine in Ex. 21, Step B, and the requisite acylating or alkylating agent in Ex. 22, the following compounds were prepared:

- 5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

Anal. calculated for $C_{36}H_{41}N_5O \cdot 0.35 H_2O$:

C, 76.39; H, 7.43; N, 12.37;

Found C, 76.39; H, 7.13; N, 12.32.

- 10 FAB MS (M+1) 560

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-cyclopropylmethyl-aminomethyl] piperidine

Anal. calculated for $C_{37}H_{43}N_5 \cdot 3.0 HCl \cdot 0.95 H_2O \cdot 0.60 CH_2Cl_2$:

- 15 C, 62.41; H, 6.73; N, 9.53;

Found C, 62.42; H, 7.02; N, 9.43.

FAB MS (M+1) 558

- 20 1-(2,2-Diphenylethyl)-3(S)-[N-(2-methyl-1H-imidazol-4-ylethyl)-N-(4-cyanobenzoyl)aminomethyl] piperidine

Anal. calculated for $C_{34}H_{37}N_5O \cdot 2.95 CF_3CO_2H \cdot 1.00 H_2O$:

C, 54.08; H, 4.77; N, 7.90;

Found C, 54.06; H, 4.74; N, 7.91.

FAB MS (M+1) 532

- 25

EXAMPLE 23

Preparation of 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylmethyl] piperidine bistrifluoroacetate

- 30

Step A: Preparation of 1-Trityl-4-(4-cyanobenzyl)-imidazole

To a suspension of activated zinc dust (3.57g, 54.98 mmol) in THF (50 mL) was added dibromoethane (0.315 mL, 3.60 mmol) and the reaction stirred under argon for 45 minutes, at 20°C. The

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suspension was cooled to 0°C and α -bromo-p-tolunitrile (9.33g, 47.6 mmol) in THF (100 mL) was added dropwise over a period of 10 minutes. The reaction was then allowed to stir at 20°C for 6 hours and bis(triphenylphosphine)Nickel II chloride (2.40g, 3.64 mmol) and 5-iodotrityl imidazole (15.95g, 36.6 mmol) were added in one portion. The resulting mixture was stirred 16 hours at 20°C and then quenched by addition of saturated NH₄Cl solution (100 mL) and the mixture stirred for 2 hours. Saturated aq. NaHCO₃ solution was added to give a pH of 8 and the solution was extracted with EtOAc (2 x 250 mL), dried (MgSO₄) and the solvent evaporated in vacuo. The residue was chromatographed (Silica gel, 0-20% EtOAc in CH₂Cl₂) to afford the title compound as a white solid.

¹H NMR (CDCl₃, 400Mz) δ (7.54 (2H, d, J=7.9Hz), 7.38(1H, s), 7.36-7.29 (11H, m), 7.15-7.09(6H, m), 6.58(1H, s) and 3.93(2H, s) ppm.

Step B: Preparation of 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylmethyl] piperidine bis trifluoroacetate bistrifluoroacetate

To a solution of 1-(2,2-Diphenylethyl)-3(S)-hydroxymethylpiperidine (Example 18, Step B) (0.271 g, 0.917 mmol) and 1-trityl-4-(4-cyanobenzyl)imidazole (0.390 g, 0.917 mmol) in CH₂Cl₂ (7 mL) was added diisopropylethylamine (0.639 mL, 3.67 mmol) under N₂. The mixture was cooled to -78 °C and trifluoromethanesulfonic anhydride (0.154 mL, 0.917mmol) was added dropwise via syringe. The cooling bath was removed and the reaction was stirred at 25 °C for 18hr. The reaction was evaporated in *vacuo* and the residue was dissolved in methanol (20mL) and heated to reflux for 1hr. After cooling the mixture was evaporated in *vacuo* and the residue was partitioned with EtOAc (50mL) and satd NaHCO₃(30mL), the organic layer separated, washed with brine (30mL) and dried (MgSO₄). Filtration and evaporation in *vacuo* gave the title compound which was purified by chromatography on silica gel using CH₂Cl₂:MeOH, 98:2, followed by preparative HPLC on a Waters C-18 Delta-pak column.

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Anal. calculated for $C_{31}H_{32}N_4 \cdot 3.10 CF_3CO_2H \cdot 0.75 H_2O$:

C, 53.98; H, 4.46; N, 6.77;

Found C, 54.02; H, 4.47; N, 6.75.

5

EXAMPLE 24

Preparation of 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylethylcarbamoyl] piperdine

- 10 Step A: Preparation of 5-(4-cyanobenzyl)-1H-imidazol-1-ylethylphthalimide
-
- 2-Hydroxyethylphthalimide (3.23 g, 16.9 mmol) was dissolved in CH_2Cl_2 (50ml) and Et_3N (3.92 mL, 28.2 mmol) under N_2 . The reaction was cooled to $-78^\circ C$ and trifluoromethanesulfonic anhydride (2.85 mL, 16.9 mmol) was added dropwise via syringe.
- 15 After stirring for 0.5 hr at $0^\circ C$ the reaction was cooled to $-20^\circ C$ and 1-trityl-4-(4-cyanobenzyl)imidazole (2.4 g, 5.64 mmol) in CH_2Cl_2 (20mL) was added to the mixture which was stirred at $25^\circ C$ for 18 hr. The reaction was concentrated in *vacuo* to dryness, and the residue was
- 20 dissolved in MeOH (75mL) and heated to reflux for 2 hr. After cooling and evaporation in *vacuo* the residue was partitioned with EtOAc (100 mL) and satd $NaHCO_3$ (30 mL). The organic layer was washed with brine (30 mL) and dried ($MgSO_4$). Evaporation in *vacuo* gave the title compound after chromatography on silica gel eluting with
- 25 CH_2Cl_2 :MeOH: NH_4OH 95:5:0.5 (3 L), 90:10:1.0 (2 L), 85:15:1.5 (3 L).

Step B: Preparation of 5-(4-cyanobenzyl)-1-(2-aminoethyl)-1H-imidazole

- 30 To a solution of 5-(4-cyanobenzyl)-1H-imidazol-1-ylethylphthalimide (3.2 g, 9.2 mmol) in absolute EtOH (75 mL) was added hydrazine (0.72 mL, 23.0 mmol), and the mixture was refluxed for 18 hr. Dimethyl phthalate (7.59 mL, 46 mmol) was added to the mixture and refluxing was continued for 4 hr. The reaction was cooled in a freezer for 18 hr. The solids that formed were filtered and washed
- 35 with water. Evaporation in *vacuo* afforded the title compound after

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chromatography on silica gel eluting with CH_2Cl_2 :MeOH: NH_4OH 95:5:0.5 (2 L), 90:10:1.0 (2 L), 85:15:1.5 (2 L).

Step C: Preparation of 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylethylcarbamoyl] piperidine

Following the procedure outlined in Example 10, Step B using 1-(2,2-Diphenylethyl)-3(S)-carboxy piperidine and the amine from Step B above, the title compound was prepared.

Anal. calculated for $\text{C}_{33}\text{H}_{35}\text{N}_5\text{O} \cdot 0.60 \text{ H}_2\text{O}$:

C, 74.99; H, 6.90; N, 13.25;

Found C, 74.99; H, 6.98; N, 13.19.

EXAMPLE 25

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., *J. Biol. Chem.* 265:14701-14704 (1990), Pompliano, et al., *Biochemistry* 31:3800 (1992) and Gibbs et al., *PNAS* U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM MgCl_2 , 5 mM dithiothreitol (DTT), 100 mM [^3H]-farnesyl diphosphate ([^3H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 $\mu\text{g/ml}$ FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvester, washed with 100% ethanol, dried and counted in an LKB β -plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^3H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound

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when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer *et al.*, Biochemistry 32:5167-5176 (1993). Human FPTase activity was
5 assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μ M ZnCl₂ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μ l of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

10 The compounds of the instant invention that are described in Example 1-24 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC₅₀ of < 10 μ M.

15 EXAMPLE 26

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The
20 assay is performed essentially as described in DeClue, J.E. *et al.*, Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemented with 10% regular DMEM, 2% fetal bovine serum and 400
25 mCi[³⁵S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM MgCl₂/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at
30 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are brought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. *et al.*, J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a

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25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 27

In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a *v-ras*, *v-raf*, or *v-mos* oncogene is tested. Cells transformed by *v-Raf* and *v-Mos* maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

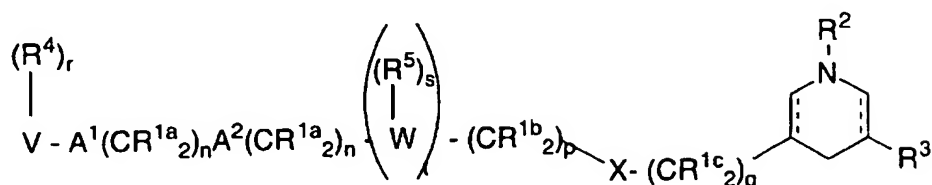
Rat 1 cells transformed with either *v-ras*, *v-raf*, or *v-mos* are seeded at a density of 1×10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

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WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula A:

5



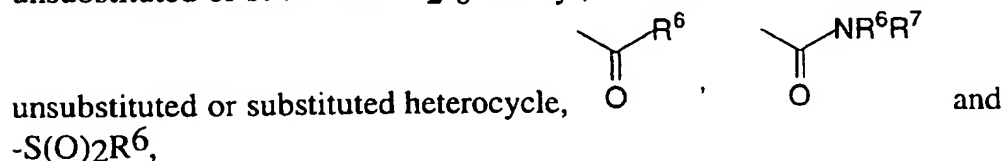
A

wherein:

R^{1a}, R^{1b} and R^{1c} are independently selected from:

- 10 a) hydrogen,
b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
15 c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocyclic, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)-NR⁸-;
20

R² is selected from: H; unsubstituted or substituted C₁₋₈ alkyl, unsubstituted or substituted C₂₋₈ alkenyl, unsubstituted or substituted aryl,



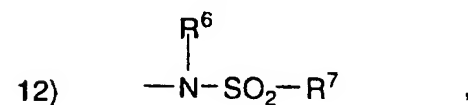
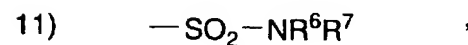
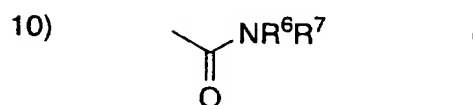
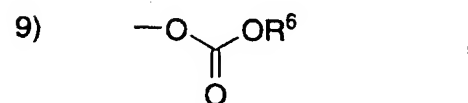
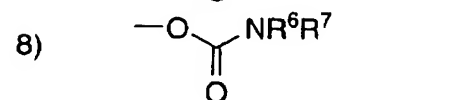
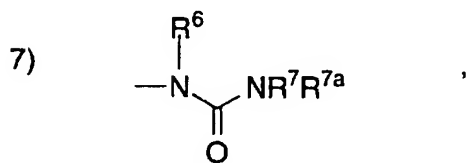
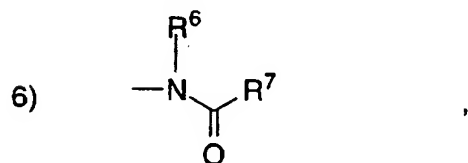
wherein the substituted group is substituted with one or more of:

- 144 -

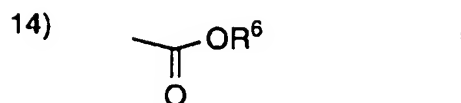
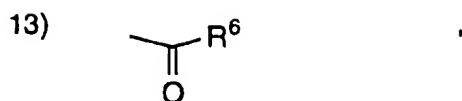
1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:

- a) C₁₋₄ alkyl,
 b) (CH₂)_pOR⁶,
 c) (CH₂)_pNR⁶R⁷,
 d) halogen,
 e) C₁₋₄ perfluoroalkyl,

- 2) C₃₋₆ cycloalkyl,
 3) OR⁶,
 4) SR⁶, S(O)R⁶, SO₂R⁶,



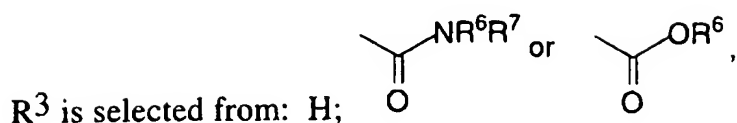
- 145 -



15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5



R^4 is independently selected from:

- 10 a) hydrogen,
 b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, R⁸₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
 15 c) C₁₋₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NH-, CN, H₂N-C(NH)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁸OC(O)NH-;

20

R^5 is independently selected from:

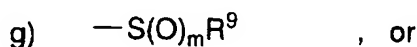
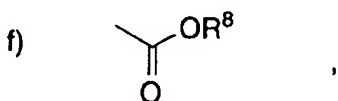
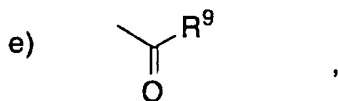
- a) hydrogen,
 b) C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₆ cycloalkyl, perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C-(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, N₃, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
 25 c) C₁₋₆ alkyl, unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-

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$C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3 , $-N(R^8)_2$, or
 $R^9OC(O)NR^8-$;

5 R^6 , R^7 and R^{7a} are independently selected from: H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, heterocycle, aryl, C₁₋₄ perfluoroalkyl, unsubstituted or substituted with one or two substituents selected from:

- 10 a) C₁₋₄ alkoxy,
 b) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle,
 c) halogen,
 d) HO,



h) $N(R^8)_2$; or

15

R^6 and R^7 may be joined in a ring;

R^7 and R^{7a} may be joined in a ring;

20 R^8 is independently selected from hydrogen, C₁₋₆ alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

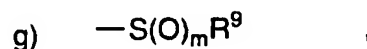
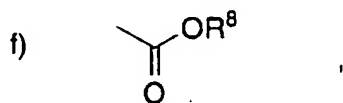
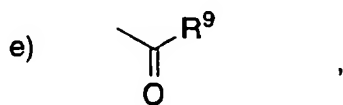
R^9 is independently selected from C₁₋₆ alkyl and aryl;

25 R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C₁₋₄ alkyl, unsubstituted or substituted C₃₋₆ cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl,

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substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- 5 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



- 10 h) N(R⁸)₂, or
 i) C₃₋₆ cycloalkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
-C(O)-, -C(O)NR⁸-, -NR⁸C(O)-, O, -N(R⁸)-,
15 -S(O)₂N(R⁸)-, -N(R⁸)S(O)₂-, or S(O)_m;

V is selected from:

- 20 a) hydrogen,
 b) heterocycle,
 c) aryl,
 d) C₁-C₂₀ alkyl wherein from 0 to 4 carbon atoms are
 replaced with a heteroatom selected from O, S, and N,
 and
 e) C₂-C₂₀ alkenyl,
25 provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen
 if A¹ is a bond, n is 0 and A² is S(O)_m;

- 148 -

W is a heterocycle;

X is a bond, $-C(=O)NR^{10}$ -, $-NR^{10}C(=O)$ -, $-S(O)_m$ -, $-NR^{10}$ -, O or $-C(=O)$ -;

5

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4;

q is 0, 1, 2, 3 or 4;

10 r is 0 to 5, provided that r is 0 when V is hydrogen;

s is 1 or 2;

t is 0 or 1; and

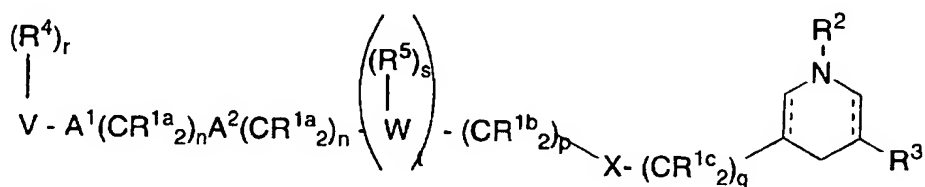
the dashed lines represent optional double bonds;

15

or an optical isomer or pharmaceutically acceptable salt thereof.

2. The compound according to Claim 1, which inhibits farnesyl-protein transferase, of the formula A:

20



A

wherein:

25 R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

R^{1b} is independently selected from:

a) hydrogen,

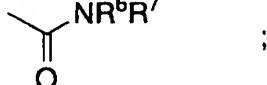
- 149 -

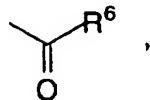
- b) unsubstituted or substituted aryl, unsubstituted or substituted heterocycle, C₃-C₆ cycloalkyl, R⁸O-, -N(R⁸)₂ or C₂-C₆ alkenyl,
- c) C₁-C₆ alkyl unsubstituted or substituted by unsubstituted or substituted aryl, heterocycle, C₃-C₆ cycloalkyl, C₂-C₆ alkenyl, R⁸O-, or -N(R⁸)₂;

R² is selected from:

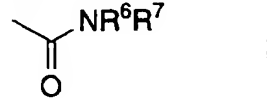
- a) C₁-8 alkyl, unsubstituted or substituted with one or more of:
- 1) aryl or heterocycle, unsubstituted or substituted with:

- i) C₁-4 alkyl,
 ii) (CH₂)_pOR⁶,
 iii) (CH₂)_pNR⁶R⁷,
 iv) halogen,
 v) C₁-4 perfluoroalkyl,

- 2) OR⁶,
 3) SR⁶, SO₂R⁶, or
 4)  ;

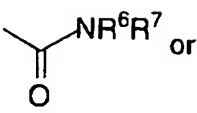
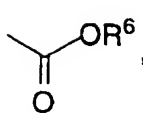
- b)  ,

- c) aryl, unsubstituted or substituted with one or more of:

- 1) C₁-8 alkyl,
 2) C₁-8 perfluoroalkyl,
 3) OR⁶,
 4) SR⁶, SO₂R⁶, or
 5)  ;

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d) $-\text{SO}_2\text{R}^6$;

R^3 is selected from: H;  or .

5 R^4 is independently selected from:

- a) hydrogen,
- b) C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

15 R^5 is selected from:

- a) hydrogen,
- b) C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 20 c) C₁-C₆ alkyl unsubstituted or substituted by C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁹S(O)_m-, R⁸C(O)NR⁸-, CN, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, R⁸OC(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

25

 R^6 , R^7 and R^{7a} are independently selected from:

H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
- 30 b) halogen, or
- c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

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R^8 is independently selected from hydrogen, C_1 - C_6 alkyl, benzyl, 2,2,2-trifluoroethyl and aryl;

R^9 is independently selected from C_1 - C_6 alkyl and aryl;

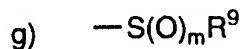
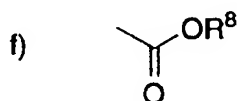
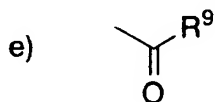
5

R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_1 -4 alkyl, unsubstituted or substituted C_3 -6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

10

- a) C_1 -4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,

15



h) $N(R^8)_2$, or

20

i) C_3 -6 cycloalkyl;

A^1 and A^2 are independently selected from: a bond, $-CH=CH-$, $-C\equiv C-$, $-C(O)-$, $-C(O)NR^8-$, O, $-N(R^8)-$, or $S(O)_m$;

25 V is selected from:

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- a) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl, and
 b) aryl;

5

W is a heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

10 X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 1, 2 or 3;

15 q is 0 or 1;

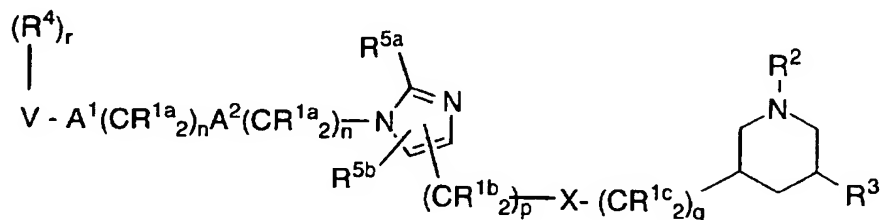
r is 0 to 5, provided that r is 0 when V is hydrogen;

s is 1 or 2; and

t is 1;

20 or an optical isomer or pharmaceutically acceptable salt thereof.

3. The compound according to Claim 1, which inhibits farnesyl-protein transferase, of the formula B:



25

B

wherein:

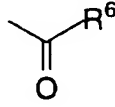
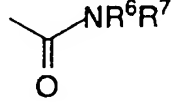
- 153 -

R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 5 a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
 c) unsubstituted or substituted C₁-C₆ alkyl wherein the
 10 substituent on the substituted C₁-C₆ alkyl is selected from unsubstituted or substituted aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O- and -N(R⁸)₂;

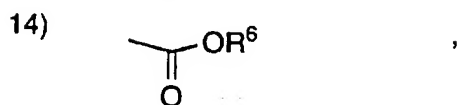
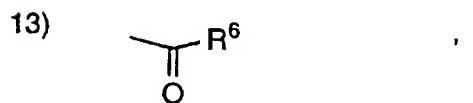
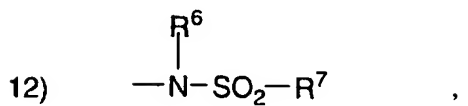
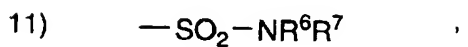
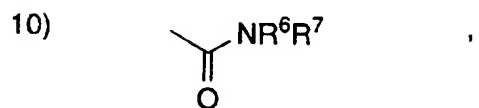
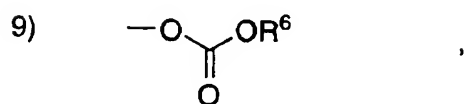
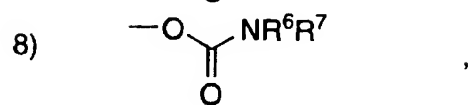
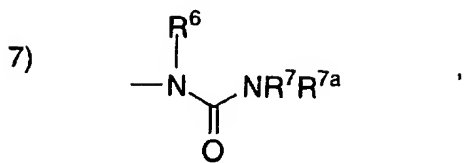
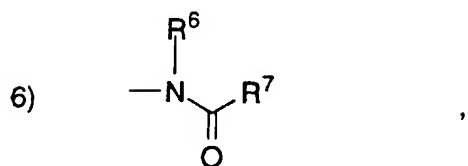
R² is selected from: H; unsubstituted or substituted C₁-8 alkyl, unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl,

- 15 unsubstituted or substituted heterocycle, ,  and
 -S(O)₂R⁶,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with
 one or two groups selected from:
 20 a) C₁-4 alkyl,
 b) (CH₂)_pOR⁶,
 c) (CH₂)_pNR⁶R⁷,
 d) halogen,
 e) C₁-4 perfluoroalkyl,
 25 2) C₃-6 cycloalkyl,
 3) OR⁶,
 4) SR⁶, S(O)R⁶, SO₂R⁶,

- 154 -

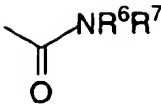
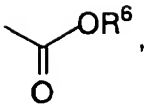


5

15) C1-8 alkyl, or

16) C1-8 perfluoroalkyl;

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R³ is selected from: H;  or .

R⁴ is independently selected from:

- a) hydrogen,
- 5 b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 10 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

15 R^{5a} and R^{5b} are independently hydrogen, C₁-C₆ alkyl, cyclopropyl, trifluoromethyl and halogen;

R⁶, R⁷ and R^{7a} are independently selected from:

- H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:
- 20 a) C₁-4 alkoxy,
 - b) halogen, or
 - c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

25 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

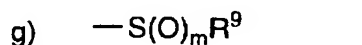
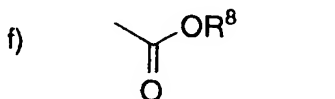
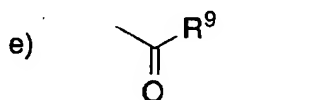
R⁹ is independently selected from C₁-C₆ alkyl and aryl;

30 R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or substituted C₁-4 alkyl, unsubstituted or substituted C₃-6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl,

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substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- 5 a) C₁₋₄ alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



- 10 h) N(R⁸)₂, or
 i) C₃₋₆ cycloalkyl;

A¹ and A² are independently selected from: a bond, -CH=CH-, -C≡C-,
 -C(O)-, -C(O)NR⁸-, O, -N(R⁸)-, or S(O)_m;

15

V is selected from:

- a) hydrogen,
 b) heterocycle selected from pyrrolidinyl, imidazolyl,
 imidazolinyl, pyridinyl, thiazolyl, pyridonyl, 2-
 20 oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl,
 triazolyl and thienyl,
 c) aryl,
 d) C_{1-C20} alkyl wherein from 0 to 4 carbon atoms are
 replaced with a heteroatom selected from O, S, and N,
 25 and
 e) C_{2-C20} alkenyl, and

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provided that V is not hydrogen if A¹ is S(O)_m and V is not hydrogen if A¹ is a bond, n is 0 and A² is S(O)_m;

X is a bond, -C(=O)NR¹⁰-, -NR¹⁰C(=O)-, -S(O)_m- or -NR¹⁰-;

5

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

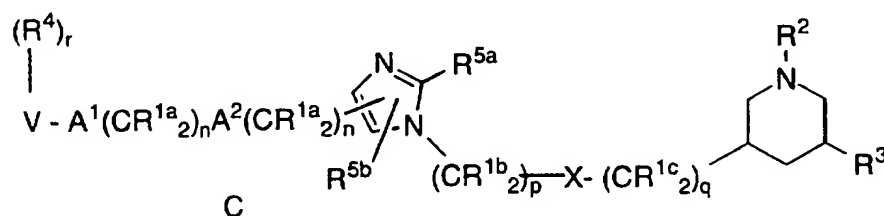
p is 0, 1, 2, 3 or 4;

q is 0 or 1; and

10 r is 0 to 5, provided that r is 0 when V is hydrogen;

or an optical isomer or pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1, which inhibits
15 farnesyl-protein transferase, of the formula C:



wherein:

20 R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₁-C₆ alkyl;

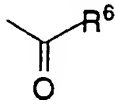
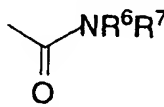
R^{1b} is independently selected from:

- 25 a) hydrogen,
b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
c) unsubstituted or substituted C₁-C₆ alkyl wherein the substituent on the substituted C₁-C₆ alkyl is selected from

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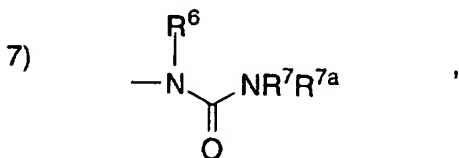
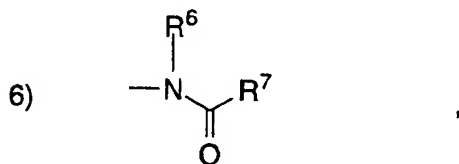
unsubstituted or substituted aryl, heterocycle, C₃-C₁₀
cycloalkyl, C₂-C₆ alkenyl, R⁸O- and -N(R⁸)₂;

- R² is selected from: H; unsubstituted or substituted C₁-8 alkyl,
5 unsubstituted or substituted C₂-8 alkenyl, unsubstituted or substituted aryl,

unsubstituted or substituted heterocycle, ,  and
-S(O)₂R⁶,

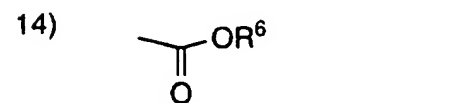
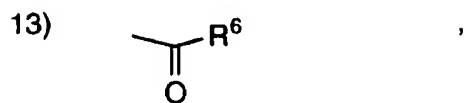
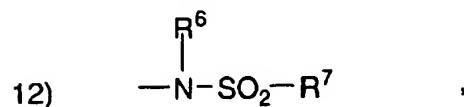
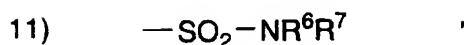
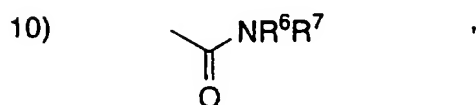
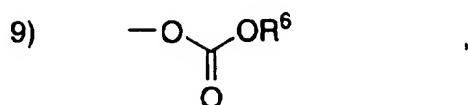
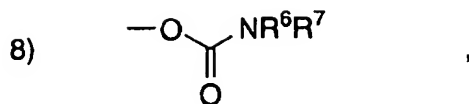
wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with
10 one or two groups selected from:
a) C₁-4 alkyl,
b) (CH₂)_pOR⁶,
c) (CH₂)_pNR⁶R⁷,
d) halogen,
15 e) C₁-4 perfluoroalkyl,
2) C₃-6 cycloalkyl,
3) OR⁶,
4) SR⁶, S(O)R⁶, SO₂R⁶,



20

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15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5

R³ is selected from: H; $\text{—C(=O)—NR}^6\text{R}^7$ or —C(=O)—OR^6 ,

R⁴ is independently selected from:

10

- a) hydrogen,
 - b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
- and

15

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- c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

- 5 R^{5a} and R^{5b} are independently hydrogen, C₁-C₆ alkyl, cyclopropyl, trifluoromethyl and halogen;

R⁶, R⁷ and R^{7a} are independently selected from:

- 10 H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle, unsubstituted or substituted with:

- a) C₁-4 alkoxy,
b) halogen, or
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

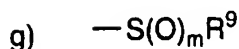
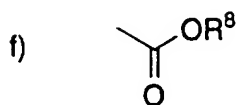
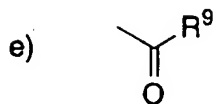
- 15 R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

- 20 R⁹ is independently selected from C₁-C₆ alkyl and aryl;

- 25 R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or substituted C₁-4 alkyl, unsubstituted or substituted C₃-6 cycloalkyl, unsubstituted or substituted heterocycle, unsubstituted or substituted aryl, substituted aroyl, unsubstituted or substituted heteroaroyl, substituted arylsulfonyl, unsubstituted or substituted heteroarylsulfonyl, wherein the substituted group is substituted with one or two substituents selected from:

- 30 a) C₁-4 alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,

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h) $\text{N(R}^8)_2$, or

i) C3-6 cycloalkyl;

5

A^1 and A^2 are independently selected from: a bond, $-\text{CH}=\text{CH}-$, $-\text{C}\equiv\text{C}-$, $-\text{C(O)}-$, $-\text{C(O)NR}^8-$, O, $-\text{N(R}^8)-$, or S(O)_m ;

V is selected from:

10

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, imidazoliny, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, oxazolyl, indolyl, quinolinyl, isoquinolinyl, triazolyl and thienyl,

15

c) aryl,

d) C_1 - C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a heteroatom selected from O, S, and N, and

e) C_2 - C_{20} alkenyl, and

20

provided that V is not hydrogen if A^1 is S(O)_m and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is S(O)_m ;

X is a bond, $-\text{C(=O)NR}^{10}-$, $-\text{NR}^{10}\text{C(=O)}-$, $-\text{S(O)}_m-$ or $-\text{NR}^{10}-$;

25

m is 0, 1 or 2;

n is 0, 1, 2, 3 or 4;

p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, $-\text{NR}^8-$ or O;

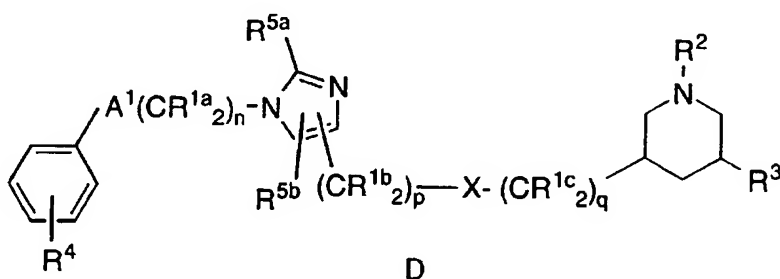
- 162 -

q is 0 or 1; and
 r is 0 to 5, provided that r is 0 when V is hydrogen;

or an optical isomer or pharmaceutically acceptable salt thereof.

5

5. The compound according to Claim 3, which inhibits farnesyl-protein transferase, of the formula D:



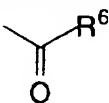
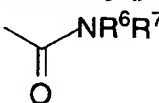
10 wherein:

R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl or C₁-C₆ alkyl;

15 R^{1b} is independently selected from:

- a) hydrogen,
 - b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
 - c) C₁-C₆ alkyl unsubstituted or substituted by aryl,
- 20 heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O-, or -N(R⁸)₂;

R² is selected from: H; unsubstituted or substituted C₁-8 alkyl,

unsubstituted or substituted aryl, ,  and -S(O)₂R⁶,

25 wherein the substituted group is substituted with one or more of:

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1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:

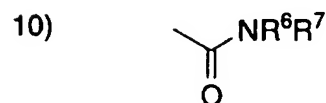
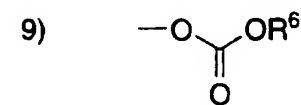
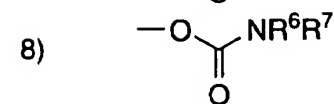
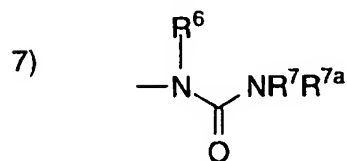
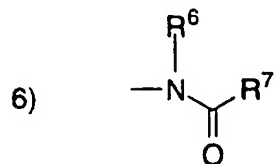
- a) C₁₋₄ alkyl,
- b) (CH₂)_pOR⁶,
- c) (CH₂)_pNR⁶R⁷,
- d) halogen,
- e) C₁₋₄ perfluoroalkyl,

2) C₃₋₆ cycloalkyl,

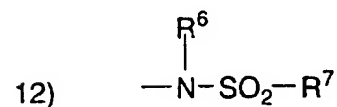
3) OR⁶,

4) SR⁶, S(O)R⁶, SO₂R⁶,

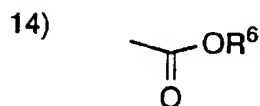
5) —NR⁶R⁷



11) —SO₂—NR⁶R⁷



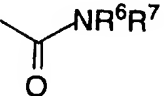
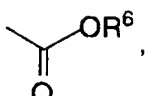
- 164 -



15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5

R³ is selected from: H;  or 

R⁴ is independently selected from:

- 10 a) hydrogen,
 b) aryl, substituted aryl, heterocycle, substituted heterocycle,
 C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₁-C₆
 perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂,
 (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-,
 and
 15 c) C₁-C₆ alkyl substituted by C₁-C₆ perfluoroalkyl, R⁸O-,
 R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or
 R⁹OC(O)NR⁸-;

20 R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

 R⁶, R⁷ and R^{7a} are independently selected from:

 H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
 unsubstituted or substituted with:

- 25 a) C₁₋₄ alkoxy,
 b) halogen, or
 c) substituted or unsubstituted aryl or substituted or
 unsubstituted heterocycle;

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R^8 is independently selected from hydrogen, C_1 - C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

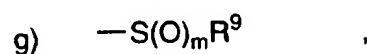
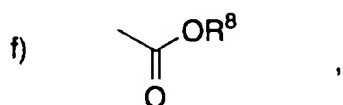
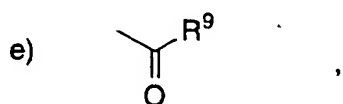
R^9 is independently selected from C_1 - C_6 alkyl and aryl;

5

R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_1 -4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

10

- a) C_1 -4 alkoxy,
- b) aryl or heterocycle,
- c) halogen,
- d) HO,



15

- h) $N(R^8)_2$, or
- i) C_{3-6} cycloalkyl;

A^1 is selected from: a bond, $-C(O)-$, O, $-N(R^8)-$, or $S(O)_m$;

20 X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

n is 0 or 1; provided that n is not 0 if A^1 is a bond, O, $-N(R^8)-$, or $S(O)_m$;

m is 0, 1 or 2;

25 p is 0, 1, 2, 3 or 4; and

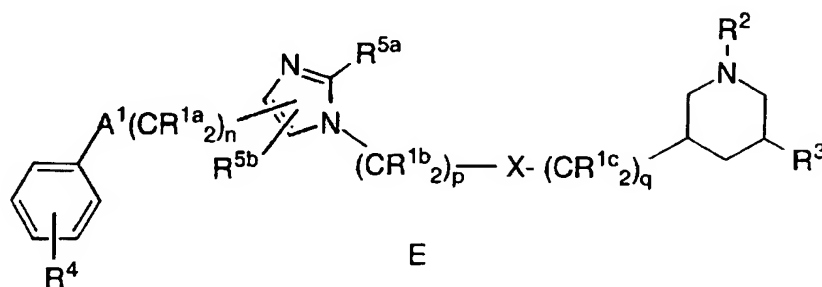
q is 0 or 1;

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or an optical isomer or pharmaceutically acceptable salt thereof.

6. The compound according to Claim 4, which inhibits farnesyl-protein transferase, of the formula E:

5



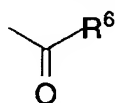
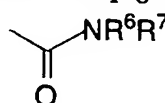
wherein:

10 R^{1a} and R^{1c} are independently selected from: hydrogen, R⁸O-,
-N(R⁸)₂, F, C₃-C₁₀ cycloalkyl or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 15 a) hydrogen,
b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R⁸O-, -N(R⁸)₂, F or C₂-C₆ alkenyl,
c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, C₂-C₆ alkenyl, R⁸O-, or -N(R⁸)₂;

20 R² is selected from: H; unsubstituted or substituted C₁-8 alkyl,

unsubstituted or substituted aryl, ,  and -S(O)₂R⁶,

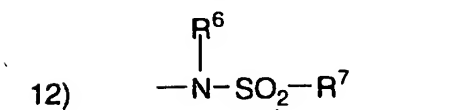
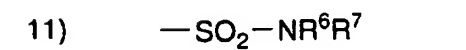
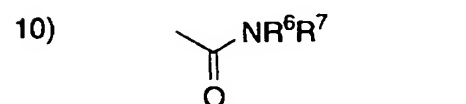
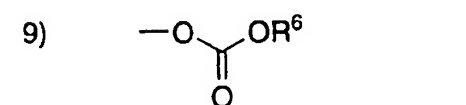
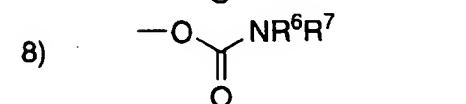
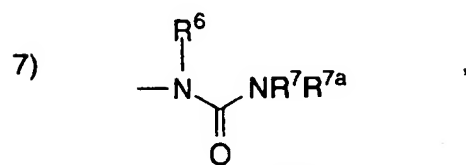
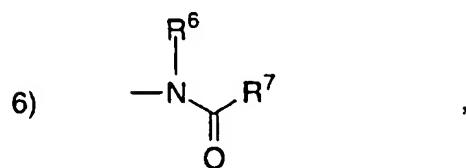
wherein the substituted group is substituted with one or more of:

- 25 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
a) C₁-4 alkyl,
b) (CH₂)_pOR⁶,

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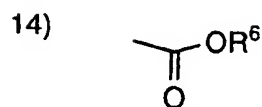
5

- c) $(\text{CH}_2)_p\text{NR}^6\text{R}^7$,
 d) halogen,
 e) C1-4 perfluoroalkyl,
 2) C3-6 cycloalkyl,
 3) OR^6 ,
 4) SR^6 , S(O)R^6 , SO_2R^6 ,



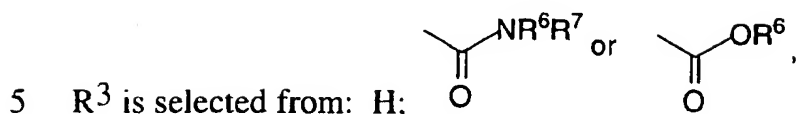
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15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;



R⁴ is independently selected from:

- a) hydrogen,
- 10 b) aryl, substituted aryl, heterocycle, substituted heterocycle, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₁₋₆ perfluoroalkyl, F, Cl, R⁸O-, R⁸C(O)NR⁸-, CN, NO₂, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-, and
- 15 c) C₁₋₆ alkyl substituted by C₁₋₆ perfluoroalkyl, R⁸O-, R⁸C(O)NR⁸-, (R⁸)₂N-C(NR⁸)-, R⁸C(O)-, -N(R⁸)₂, or R⁹OC(O)NR⁸-;

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

- 20 R⁶, R⁷ and R^{7a} are independently selected from:
H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:
- a) C₁₋₄ alkoxy,
- b) halogen, or
- 25 c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

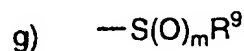
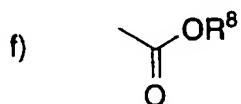
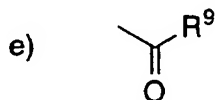
R⁸ is independently selected from hydrogen, C₁₋₆ alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

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R^9 is independently selected from C_1 - C_6 alkyl and aryl;

R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_1 -4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

- a) C_1 -4 alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



h) $N(R^8)_2$, or

i) C_3 -6 cycloalkyl;

15

X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

n is 0 or 1;

m is 0, 1 or 2;

20 p is 0, 1, 2, 3 or 4, provided that p is not 0 if X is a bond, $-NR^8-$ or O; and

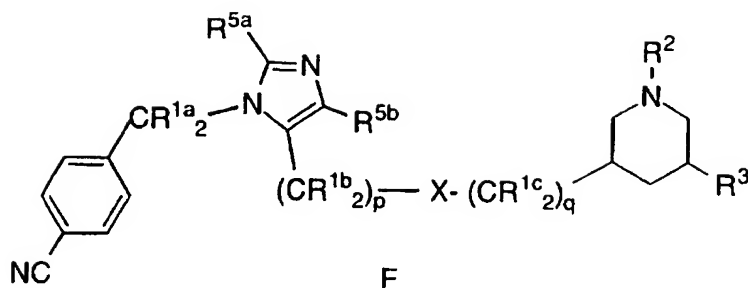
q is 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

25

7. The compound according to Claim 5, which inhibits farnesyl-protein transferase, of the formula F:

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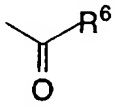
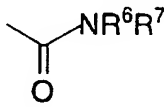
wherein:

- 5 R^{1a} and R^{1c} are independently selected from: hydrogen, C₃-C₁₀ cycloalkyl or C₁-C₆ alkyl;

R^{1b} is independently selected from:

- 10 a) hydrogen,
 b) aryl, heterocycle, C₃-C₁₀ cycloalkyl, R^8O- , $-N(R^8)_2$ or F,
 c) C₁-C₆ alkyl unsubstituted or substituted by aryl, heterocycle, C₃-C₁₀ cycloalkyl, R^8O- , or $-N(R^8)_2$;

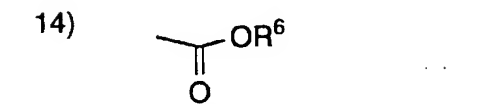
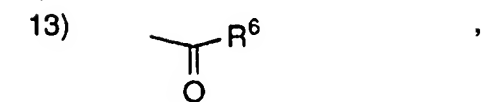
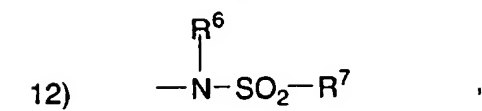
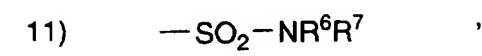
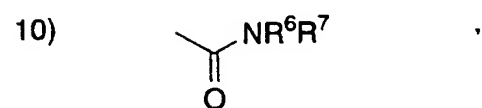
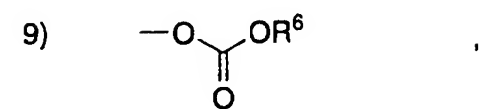
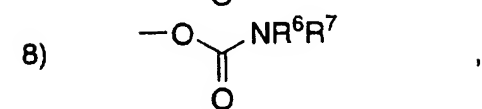
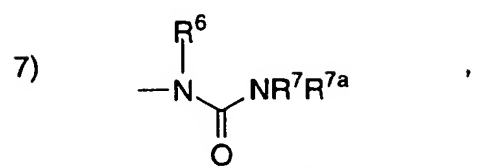
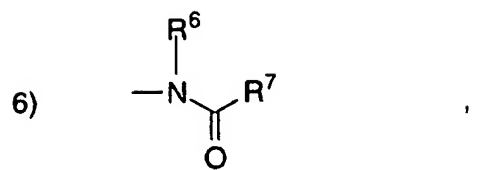
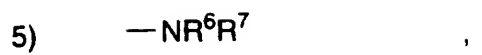
R^2 is selected from: H; unsubstituted or substituted C₁-8 alkyl,

- 15 unsubstituted or substituted aryl, ,  and $-S(O)_2R^6$,

wherein the substituted group is substituted with one or more of:

- 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:
 20 a) C₁-4 alkyl,
 b) $(CH_2)_pOR^6$,
 c) $(CH_2)_pNR^6R^7$,
 d) halogen,
 e) C₁-4 perfluoroalkyl,
 2) C₃-6 cycloalkyl,
 25 3) OR^6 ,
 4) SR^6 , $S(O)R^6$, SO_2R^6 ,



- 171 -



15) C₁-8 alkyl, or

16) C₁-8 perfluoroalkyl;

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R³ is selected from: H;  or ,

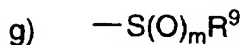
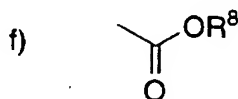
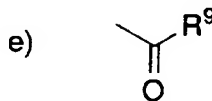
R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

- 5 R⁶, R⁷ and R^{7a} are independently selected from:
 H; C₁-4 alkyl, C₃-6 cycloalkyl, aryl, heterocycle,
 unsubstituted or substituted with:
 a) C₁-4 alkoxy,
 b) halogen, or
 10 c) substituted or unsubstituted aryl or substituted or
 unsubstituted heterocycle;

R⁸ is independently selected from hydrogen, C₁-C₆ alkyl, 2,2,2-
 trifluoroethyl, benzyl and aryl;

- 15 R⁹ is independently selected from C₁-C₆ alkyl and aryl;

- R¹⁰ is selected from: H; R⁸C(O)-; R⁹S(O)_m-; unsubstituted or
 substituted C₁-4 alkyl, wherein the substituted alkyl group is substituted
 20 with one or two substituents selected from:
 a) C₁-4 alkoxy,
 b) aryl or heterocycle,
 c) halogen,
 d) HO,



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- h) $N(R^8)_2$, or
 i) C₃₋₆ cycloalkyl;

5 X is a bond, $-C(=O)NR^{10}$ -, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

m is 0, 1 or 2;

p is 0, 1, 2, 3 or 4; and

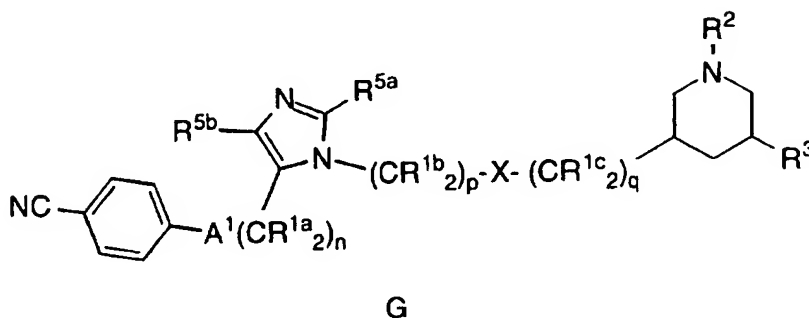
q is 0 or 1;

10

or an optical isomer or pharmaceutically acceptable salt thereof.

8. The compound according to Claim 6, which inhibits
 farnesyl-protein transferase, of the formula G:

15



wherein:

20 R^{1a} and R^{1c} are independently selected from: hydrogen, R⁸O-,
 $-N(R^8)_2$, F, C₃₋₁₀ cycloalkyl or C₁₋₆ alkyl;

R^{1b} is independently selected from:

- 25 a) hydrogen,
 b) aryl, heterocycle or C₃₋₁₀ cycloalkyl,
 c) C₁₋₆ alkyl unsubstituted or substituted by aryl,
 heterocycle, C₃₋₁₀ cycloalkyl, C₂₋₆ alkenyl, R⁸O-, or
 $-N(R^8)_2$;

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R^2 is selected from: H; unsubstituted or substituted C_{1-8} alkyl,

unsubstituted or substituted aryl, $\begin{array}{c} \text{R}^6 \\ \diagup \\ \text{C} \\ \parallel \\ \text{O} \end{array}$, $\begin{array}{c} \text{NR}^6\text{R}^7 \\ \diagup \\ \text{C} \\ \parallel \\ \text{O} \end{array}$ and $-\text{S}(\text{O})_2\text{R}^6$,

wherein the substituted group is substituted with one or more of:

5 1) aryl or heterocycle, unsubstituted or substituted with one or two groups selected from:

- a) C_{1-4} alkyl,
 b) $(\text{CH}_2)_p\text{OR}^6$,
 c) $(\text{CH}_2)_p\text{NR}^6\text{R}^7$,
 d) halogen,
 e) C_{1-4} perfluoroalkyl,

10

- 2) C_{3-6} cycloalkyl,
 3) OR^6 ,
 4) SR^6 , $\text{S}(\text{O})\text{R}^6$, SO_2R^6 ,

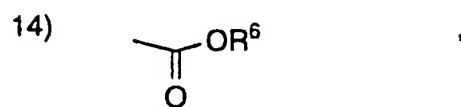
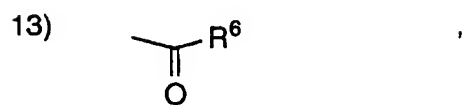
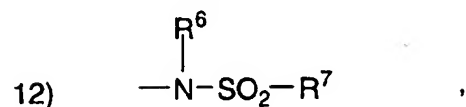
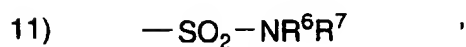
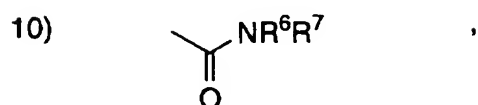
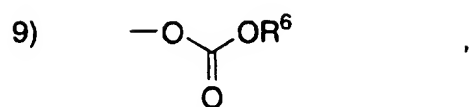
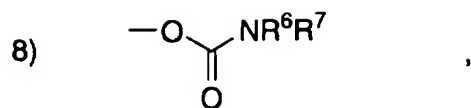
15

5) $-\text{NR}^6\text{R}^7$,

6) $\begin{array}{c} \text{R}^6 \\ | \\ -\text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{R}^7 \\ \parallel \\ \text{O} \end{array}$,

7) $\begin{array}{c} \text{R}^6 \\ | \\ -\text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{NR}^7\text{R}^{7a} \\ \parallel \\ \text{O} \end{array}$,

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15) C₁₋₈ alkyl, or

16) C₁₋₈ perfluoroalkyl;

5

R³ is selected from: H; $\text{—C(=O)—NR}^6\text{R}^7$ or —C(=O)—OR^6 ,

R^{5a} and R^{5b} are independently hydrogen, ethyl, cyclopropyl or methyl;

10

R⁶, R⁷ and R^{7a} are independently selected from:

H; C₁₋₄ alkyl, C₃₋₆ cycloalkyl, aryl, heterocycle,
unsubstituted or substituted with:

a) C₁₋₄ alkoxy,

b) halogen, or

15

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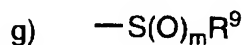
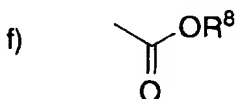
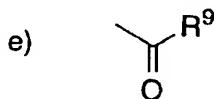
c) substituted or unsubstituted aryl or substituted or unsubstituted heterocycle;

5 R^8 is independently selected from hydrogen, C_1 - C_6 alkyl, 2,2,2-trifluoroethyl, benzyl and aryl;

R^9 is independently selected from C_1 - C_6 alkyl and aryl;

10 R^{10} is selected from: H; $R^8C(O)-$; $R^9S(O)_m-$; unsubstituted or substituted C_1 -4 alkyl, wherein the substituted alkyl group is substituted with one or two substituents selected from:

- 15 a) C_1 -4 alkoxy,
b) aryl or heterocycle,
c) halogen,
d) HO,



h) $N(R^8)_2$, or

i) C_3 -6 cycloalkyl;

20

A^1 is selected from: a bond, $-C(O)-$, O, $-N(R^8)-$, or $S(O)_m$;

X is a bond, $-C(=O)NR^{10}-$, $-NR^{10}C(=O)-$, $-S(O)_m-$ or $-NR^{10}-$;

25 m is 0, 1 or 2;

n is 0 or 1;

p is 1, 2 or 3; and

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q is 0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

5 9. A compound which inhibits farnesyl-protein transferase which is:

1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10

1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(1-Naphthylmethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15

1-Benzyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20

1-Methyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Indanyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25

1-(2-Diphenylethyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Phenylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30

1-(2-Methylpropyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35

1-Phenethyl-*cis*-3-carboxyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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- 1-Phenethyl-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]piperidine
- 5 1-Phenethyl-*cis*-3-[N-(benzyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-Phenethyl-*cis*-3-[N-(cyclopropyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 10 1-Phenethyl-*cis*-3-[N-(*t*-butyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1- (2,2-Diphenylethyl)-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 15 1- (2,2-Diphenylethyl)-*cis*-3-[N-(*t*-butyl)carbamyl]-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 20 N-[1-Phenethyl-*cis*-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamyl] piperidine-3-carbonyl] methionine methyl ester
- N-[1-Phenethyl-*cis*-5-(N'-(4-cyanobenzyl)-1-imidazol-5-ylethyl)carbamyl] piperidine-3-carbonyl] methionine
- 25 1-(*t*-Butoxycarbonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine
- 1-Phenethyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine
- 30 1-Diphenylacetyl-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 35 1-(*t*-Butoxycarbonyl)-*trans*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl]-piperidine

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1-(2,2-Diphenylethyl)-3-[N-1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylacetyl)amino] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylpropionyl)amino] piperidine

10 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylcarbonyl)amino] piperidine

15 1-(Phenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(Diphenylacetyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(3-Chlorobenzoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(3-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(Dibenzylsuberylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2-(3-Methylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(3-Trifluoromethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(2-(2-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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1-(2-(4-Chlorophenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2-(3-Aminomethylphenyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Phenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-(2-Phenethyl)-3(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-(3-Phenylpropyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Benzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(2-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(3-Chlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2,2-Diphenyl-2-hydroxyethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Methoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(3,5-Dichlorobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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1-(3-Trifluoromethoxybenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(2,5-Dimethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(3-Trifluoromethylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-(3-Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-Isobutyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(2-Methyl-2-phenylethyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

25 1-(2-(1-Piperidinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

30 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-methoxybenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

35 1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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- 1-(3-Methoxyphenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 5 1-(1-Naphthylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(3-Chlorophenethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 10 1-(α -Methylbenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 15 1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(α -Toluenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 20 1-(Benzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(1-Naphthylenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 25 1-(3-Chlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 1-(3,5-Dichlorobenzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 30 1-(α -Toluenesulfonyl)-3-(R)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine
- 35 1-(α -Toluenesulfonyl)-*cis*-3-methoxycarbonyl-5-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

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1-(Methanesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

5 1-(Diphenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(Phenylcarbamoyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

10 1-[2-(2-Pyridyl)-2-phenyl-2-hydroxyethyl]-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2-Pyridylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

15 1-Phenyl-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

20 1-(3-Methylphenyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[2-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethylthiomethyl] piperidine

25 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethylsulfonylmethyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-methyl-carbamoyl] piperidine

30 1-(3-Bromobenzyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)N-methyl-carbamoyl] piperidine

35 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)aminomethyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

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1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

5 1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-cyclopropylmethyl-aminomethyl] piperidine

1-(2,2-Diphenylethyl)-3(S)-[N-(2-methyl-1H-imidazol-4-ylethyl)-N-(4-cyanobenzoyl)aminomethyl] piperidine

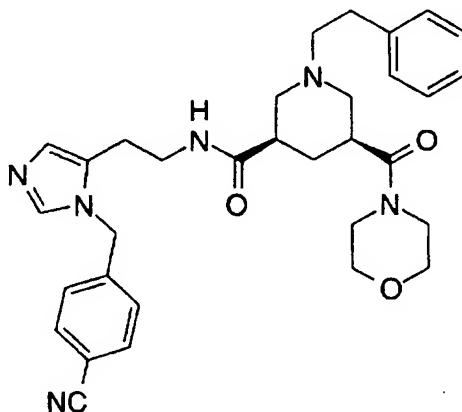
10 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylmethyl] piperidine

15 1-(2,2-Diphenylethyl)-3(S)-[5-(4-cyanobenzyl)-1H-imidazol-1-ylethylcarbamoyl] piperidine

or an optical isomer or a pharmaceutically acceptable salt thereof.

10. The compound according to Claim 9 which is:

20 1-Phenethyl-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(4-cyanobenzyl)-1-imidazole-5-ethyl)carbamyl]piperidine



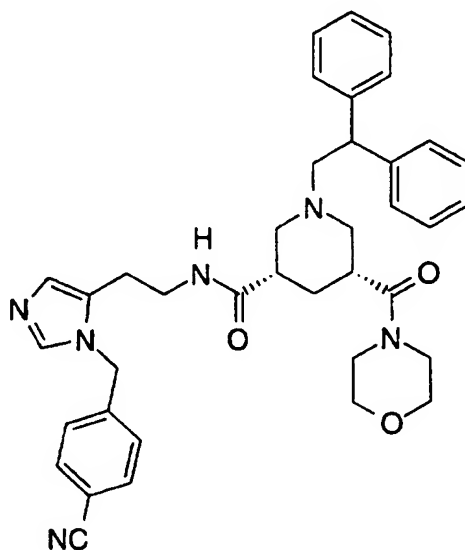
25 or an optical isomer or a pharmaceutically acceptable salt thereof.

11. The compound according to Claim 9 which is:

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1-(2-Diphenylethyl)-*cis*-3-[N-(1-morpholinyl)carbamyl]-5-[N-(4-cyanobenzyl-1-imidazole-5-ethyl)carbamyl] piperidine

5



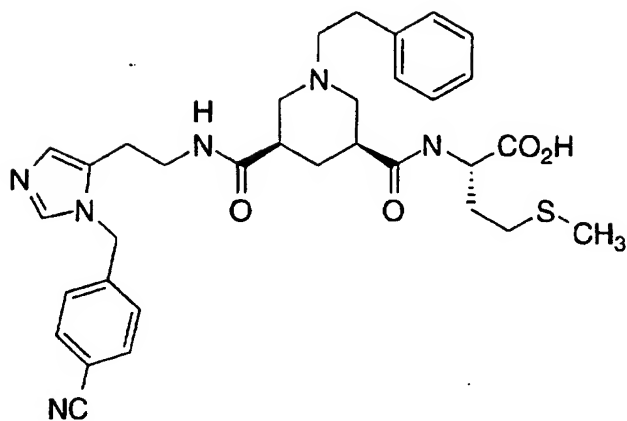
or an optical isomer or a pharmaceutically acceptable salt thereof.

12. The compound according to Claim 9 which is:

10

N-[1-Phenethyl-5-(N'-(4-cyanobenzyl-1-imidazole-5-ethyl)carbamyl) piperidine-3-carbonyl] methionine

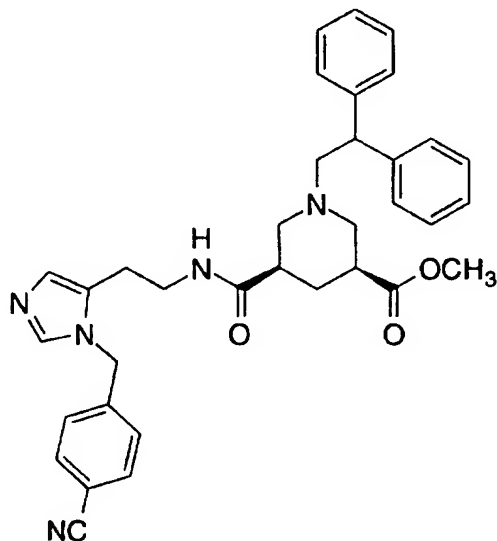
- 186 -



or an optical isomer or a pharmaceutically acceptable salt thereof.

5 13. The compound according to Claim 9 which is:

1-(2-Diphenylethyl)-3-methoxycarbonyl-5-[N-(4-cyanobenzyl)-1-imidazole-5-ethyl]carbonyl] piperidine



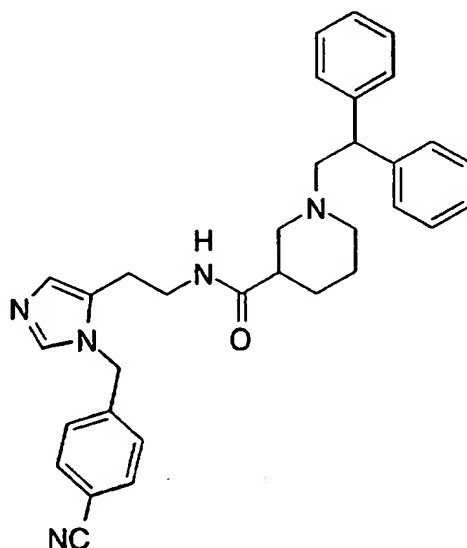
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or an optical isomer or a pharmaceutically acceptable salt thereof.

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14. The compound according to Claim 9 which is:

1-(2,2-Diphenylethyl)-*cis*-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
5 ylethyl)carbamoyl] piperidine



or an optical isomer or a pharmaceutically acceptable salt thereof.

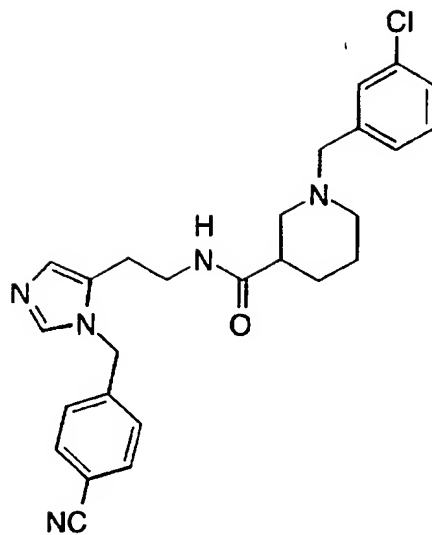
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15. The compound according to Claim 9 which is:

1-(3-Chlorobenzyl)-3-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-
15 ylethyl)carbamoyl] piperidine

15

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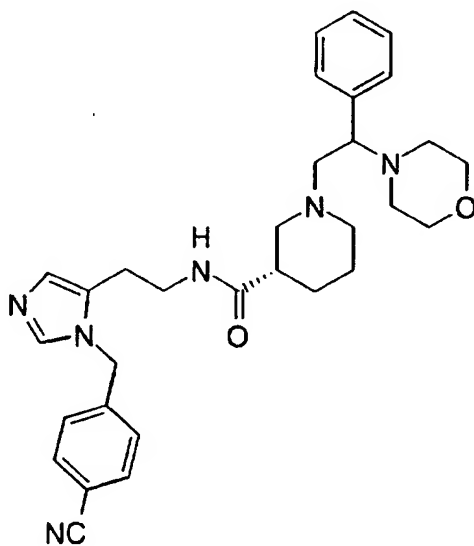


or an optical isomer or a pharmaceutically acceptable salt thereof.

5

16. The compound according to Claim 9 which is:

1-(2-(1-Morpholinyl)-2-phenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine



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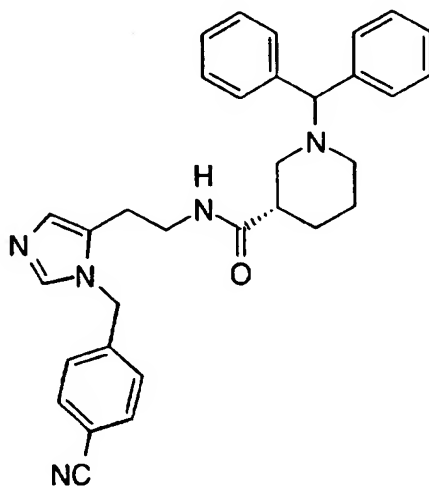
- 189 -

or an optical isomer or a pharmaceutically acceptable salt thereof.

17. The compound according to Claim 9 which is:

5

1-(Diphenylmethyl)-3(S)-[N-(1-(4-cyanobenzyl)-2-methyl-1H-imidazol-5-ylethyl)carbamoyl] piperidine

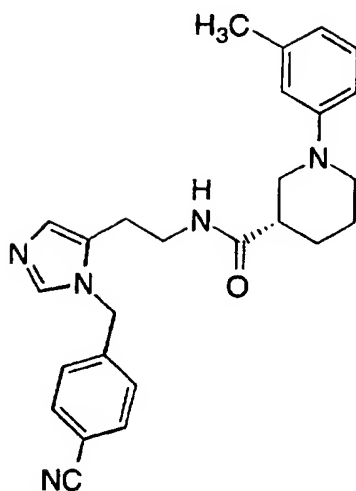


10 or an optical isomer or a pharmaceutically acceptable salt thereof.

18. The compound according to Claim 9 which is:

15 1-(3-Methylphenyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)carbamoyl] piperidine

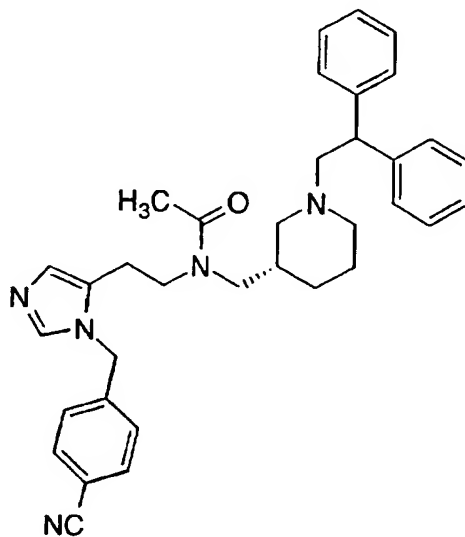
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or an optical isomer or a pharmaceutically acceptable salt thereof.

5 19. The compound according to Claim 9 which is:

1-(2,2-Diphenylethyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-ylethyl)-N-acetyl-aminomethyl] piperidine

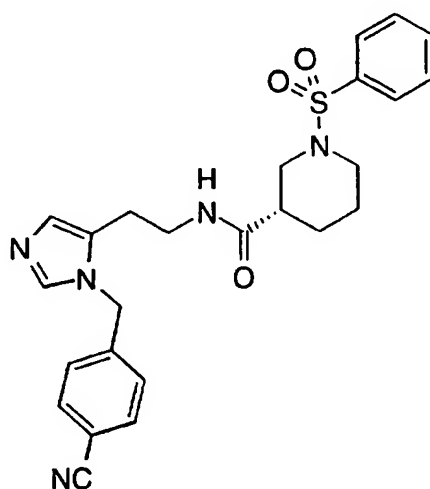


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or an optical isomer or a pharmaceutically acceptable salt thereof.

20. The compound according to Claim 9 which is:

- 5 1-(Benzenesulfonyl)-3(S)-[N-(1-(4-cyanobenzyl)-1H-imidazol-5-yl)ethyl]carbamoyl] piperidine



or an optical isomer or a pharmaceutically acceptable salt thereof.

10

21. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

15

22. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 5.

20

23. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

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24. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 9.

5 25. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

10 26. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 22.

15 27. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 23.

20 28. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 24.

 29. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

25 30. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 22.

30 31. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 23.

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32. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 24.

5 33. A method for treating neurofibromin benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

10 34. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

15 35. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

20 36. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

25 37. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 21.

 38. A pharmaceutical composition made by combining the compound of Claim 1 and a pharmaceutically acceptable carrier.

30 39. A process for making a pharmaceutical composition comprising combining a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18811

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/445; C07D 401/12

US CL : 546/210; 514/326

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/210; 514/326

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3,038,835 A (ENDRES ET AL.) 12 June 1962 (12.06.62), see entire document, especially column 1.	1-39 (in part)
A, P	US 5,476,942 A (LASSALLE ET AL.) 19 December 1995 (19.12.95), see entire document, especially column 1.	1-39 (in part)

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

B earlier document published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T

later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

G

document member of the same patent family

Date of the actual completion of the international search

07 FEBRUARY 1997

Date of mailing of the international search report

04 MAR 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

R. W. RAMSUER

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18811

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-39 (in part)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/18811

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. R2, R3, R4, R5, R6, R7, V, W, X, etc.) result in claimed subject matter that is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the art. The subject matter claimed contains a -N- group which does not define a contribution over the prior art. Therefore, the first discernable invention as found in Example 1 (the compound therein, the pharmaceutical composition therewith, the method treating colorectal carcinoma) has been searched.